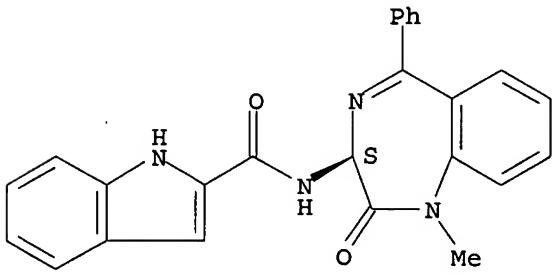
L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2004 ACS on STN
RN 103420-77-5 REGISTRY
CN 1H-Indole-2-carboxamide, N-[(3S)-2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-1,4-Benzodiazepine, 1H-indole-2-carboxamide deriv.
CN 1H-Indole-2-carboxamide, N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-, (S)-
OTHER NAMES:
CN Devacade
CN **Devazepide**
CN L 364718
CN MK 329
FS STEREOSEARCH
MF C25 H20 N4 O2
SR CA
LC STN Files: ADISINSIGHT, AGRICOLA, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, DDFU, DRUGU, EMBASE, IMSDRUGNEWS, IMSRESEARCH, IPA, MEDLINE, NIOSHTIC, PHAR, PROMT, PROUSDDR, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: WHO
DT.CA CAplus document type: Conference; Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); PROC (Process); RACT (Reactant or reagent); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
RLD.NP Roles for non-specific derivatives from non-patents: PREP (Preparation)

Absolute stereochemistry. Rotation (-).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

288 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
289 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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=> file caplus medline biosis embase uspatful
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     6.62       6.83

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=> s devazepide or devacade or l 364718 or mk 329 or 103420-77-5/rn
'RN' IS NOT A VALID FIELD CODE
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L2        3393 DEVAZEPIDE OR DEVACADE OR L 364718 OR MK 329 OR 103420-77-5/RN

=> s l2 and (opioid or opiate or meperidine or pentazocine or dextromoramide or
diphenoxylate or dipipanone or morphine or nalbuphine or methadone or dipipanone or
meptazinol or phenazocine or tramadol or remifentanil)
L3         315 L2 AND (OPIOID OR OPIATE OR MEPERIDINE OR PENTAZOCINE OR DEXTROM
               ORAMIDE OR DIPHENOXYLATE OR DIPIPANONE OR MORPHINE OR NALBUPHINE
                OR METHADONE OR DIPIPANONE OR MEPTAZINOL OR PHENAZOCINE OR
               TRAMADOL OR REMIFENTANIL)

=> dup rem l3
PROCESSING COMPLETED FOR L3
L4          166 DUP REM L3 (149 DUPLICATES REMOVED)

=> focus
PROCESSING COMPLETED FOR L4
L5          166 FOCUS L4 1-

=> s l5 and (adverse effect or side effect or constipation or dizziness or
tiredenss or fatigue or vomitting or nausea)
   4 FILES SEARCHED...
L6          38 L5 AND (ADVERSE EFFECT OR SIDE EFFECT OR CONSTIPATION OR DIZZIN
               ESS OR TIREDENSS OR FATIGUE OR VOMITTING OR NAUSEA)

=>
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L7 ANSWER 28 OF 38 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

ACCESSION NUMBER: 2002460417 EMBASE
TITLE: Abdominal vagal afferent neurones: An important target for the treatment ofgastrointestinal dysfunction.
AUTHOR: Andrews P.L.R.; Sanger G.J.
CORPORATE SOURCE: P.L.R. Andrews, Department of Physiology, St George's Hospital Medical School, Cranmer Terrace, London SW17 0RE, United Kingdom. pandrews@sghms.ac.uk
SOURCE: Current Opinion in Pharmacology, (1 Dec 2002) 2/6 (650-656).
Refs: 53
ISSN: 1471-4892 CODEN: COPUBK
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Vagal afferents are extensively distributed in the digestive tract from the oesophagus to the colon. They are involved in the reflex control of normal gastrointestinal (GI) tract function (e.g. secretion and motility) as well as reflexes more characteristic of diseases such as functional dyspepsia and gastroesophageal reflux disease (e.g. vomiting, disordered lower esophageal sphincter relaxation and gastric accommodation). They are also implicated in signalling non-painful sensations (e.g. **nausea** and early satiety) associated with disease. A variety of receptors has been identified on vagal afferents, which can either enhance (e.g. 5-HT(3), CCK(1), VR(1) and NK(1) receptors) or reduce (e.g. ghrelin, leptin, k-**opioid** and GABA(B) receptors) activity, offering a range of potential therapeutic targets. Commonly used laboratory species (e.g. rat and mouse) lack an emetic reflex, and the implications of this for models of upper GI disorders have been explored in the light of expanding knowledge of the neuropharmacology of the emetic reflex implicating glutamate, prostanoids, cannabinoids and substance P. Additional pathophysiological roles for vagal afferents (e.g. in thermoregulation, arousal and **fatigue**) are being investigated, raising the intriguing possibility of the vagus as a target in non-GI disorders.

L7 ANSWER 26 OF 38 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 2002:79521 BIOSIS
DOCUMENT NUMBER: PREV200200079521
TITLE: Systemic pharmacomodulation of transient lower esophageal sphincter relaxations.
AUTHOR(S): Holloway, Richard H. [Reprint author]
CORPORATE SOURCE: Department of Gastroenterology, Hepatology, and General Medicine, Royal Adelaide Hospital, Department of Medicine, University of Adelaide, Adelaide, South Australia, Australia
SOURCE: American Journal of Medicine, (December 3, 2001) Vol. 111, No. Supplement 8A, pp. 178S-185S. print.
CODEN: AJMEAZ. ISSN: 0002-9343.
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 16 Jan 2002
Last Updated on STN: 25 Feb 2002

AB Transient lower esophageal sphincter relaxations (TLESRs) are the major mechanism of reflux in patients with gastroesophageal reflux disease. They are therefore attractive targets for pharmacotherapy. During the past 5 years, there has been a burgeoning interest in the neural pathways that control these events and in the pharmacologic receptors involved in these pathways. Several agents have been shown to reduce the rate of TLESRs, including cholecystokinin-A antagonists, anticholinergic agents, nitric oxide synthase inhibitors, **morphine**, somatostatin, serotonin type 3-receptor antagonists, and gamma-aminobutyric acid-B (GABAB) agonists. Their predominant site of action appears to be on either the afferent pathways and/or the central integrative mechanisms within the dorsal vagal complex in the brainstem. Most of the agents tested are unsuitable for clinical use either because of **side effects** or because of the lack of an orally effective formulation. The most promising agents identified to date are the GABAB agonists. Baclofen, the prototype GABAB agonist, inhibits the rate of TLESRs by more than 50%. Control of TLESRs is a major new approach to the treatment of reflux disease. It is likely to be applicable to the majority of patients, particularly those without macroscopic mucosal lesions or only mild erosive disease. Further development of more effective agents will depend both on a better understanding of the neural pathways and receptors involved in the control of TLESRs, as well as on investigation of other novel agents. At present, inhibition of TLESRs is at the threshold of transition from concept to practical use. Whether it makes the final leap into the mainstream of therapy will depend on the development of new, novel, and well-targeted pharmacologic agents.

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ACCESSION NUMBER: 93252437 EMBASE
DOCUMENT NUMBER: 1993252437
TITLE: Therapeutic potential of cholecystokinin receptor antagonists in CNS disorders.
AUTHOR: Schiantarelli P.
CORPORATE SOURCE: Preclinical Research Division, Boehringer Ingelheim Italy, Via Serio 15,20139 Milano, Italy
SOURCE: Pharmacological Research, (1993) 28/1 (1-9).
ISSN: 1043-6618 CODEN: PHMREP
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
030 Pharmacology
032 Psychiatry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB CCK is a central neurotransmitter which modulates dopaminergic transmission in different CNS areas; such modulation can be selectively mediated either by CCKA or CCK-B subtypes, which corresponds to the subtypes previously categorized as 'peripheral' and 'central' CCK receptors, respectively. Therefore, selective CCK-A or CCK-B receptor antagonists are putatively useful in neuropsychiatric disorders associated with changes in dopaminergic tone. CCK-A antagonists might be effective in psychosis and drug addiction/reward, two pathological conditions characterized by DA hyperactivity in mesolimbic areas, although a potential effect of CCK-B antagonists in schizophrenia has also been suggested. CCK-B antagonists might potentiate the effects of dopaminergic agonist therapy in Parkinson's disease. At the present status of knowledge it is premature to predict the real clinical potential of the CCK antagonists in the abovementioned indications, it can be theoretically assumed, however, that a total or partial replacement of the classical D-2 dopamine antagonist neuroleptics in psychosis, and of the dopaminergic agonists in Parkinson's disease, could eliminate or reduce the **side-effects** typical of these drugs. Similarly, CCK-B antagonists could be given in combination with the **opioid** analgesics with a possible reduction of the dosage and **side-effects** of the latter drugs. A body of preclinical evidence indicates towards CCK-B receptor antagonists promising antianxiety potential. They show to be effective in a wide spectrum of anxiolytic-like animal models, appearing, in addition, to be devoid of tolerance liability, withdrawal symptoms and sedative effects.

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ACCESSION NUMBER: 92104144 EMBASE
DOCUMENT NUMBER: 1992104144
TITLE: Neuropeptides. Function and clinical applications.
AUTHOR: Hughes J.; Woodruff G.N.
CORPORATE SOURCE: Parke-Davis Neuroscience Research Centre, Hills Road, Cambridge, CB2 2QB, United Kingdom
SOURCE: Arzneimittel-Forschung/Drug Research, (1992) 42/2 A (250-255).
ISSN: 0004-4172 CODEN: ARZNAD
COUNTRY: Germany
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 002 Physiology
032 Psychiatry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English; German

AB Neuropeptides are the most abundant chemical messengers in the brain and their major role seems to be the modulation of amine and amino acid neurotransmission. This appears to be achieved at many sites by the co-release of peptide with the primary transmitter. The presynaptic biochemistry and physiology of neuropeptides ensure that neuromodulation is highly plastic with almost infinite adaptive potential. The recent development of novel drugs (termed peptoids) that mimic or block neuropeptide function have opened up new clinical approaches to a number of conditions. Thus high efficacy kappa **opioid**-receptor agonists such as CI-977 (enadoline) have potential for the treatment of pain and stroke whilst the development of highly selective and bioavailable cholecystokinin B (CCK-B) antagonists such as CI-988([R-(R*,R*)]-4-[[2 [[3-(1H-indol- 3-yl)-2-methyl-1-ox6-2-[[tricyclo[3.3.1.1.3.1]dec-2-yloxy)carbonyl]amino]propyl]amino]-1-phenethyl]amino-4-oxobutanoic acid) have offered new insights into the mechanisms underlying and the treatment of anxiety disorders and drug abuse. In general it appears that peptoids may offer a greater selectivity of drug action when compared to amino acid/amine based compounds. Peptoid antagonists appear to be relatively free of **side effects** possibly because neuropeptide systems are only activated under very selective conditions. Peptoid agonists on the other hand can exert extremely powerful actions on brain function and this may be related to the key position neuropeptide receptors occupy in the hierarchy of chemical communication in the brain.

L7 ANSWER 22 OF 38 MEDLINE on STN
ACCESSION NUMBER: 93379229 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8369487
TITLE: Association of the peptidase inhibitor RB 101 and a CCK-B antagonist strongly enhances antinociceptive responses.
AUTHOR: Maldonado R; Derrien M; Noble F; Roques B P
CORPORATE SOURCE: Departement de Pharmacochomie Moleculaire et Structurale, INSERM U266-CNRS URA D1500, Universite Rene Descartes, Faculte des Sciences, Pharmaceutiques et Biologiques, Paris, France.
SOURCE: Neuroreport, (1993 Jul) 4 (7) 947-50.
Journal code: 9100935. ISSN: 0959-4965.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199310
ENTRY DATE: Entered STN: 19931029
Last Updated on STN: 19990129
Entered Medline: 19931008

AB The brain peptide cholecystokinin (CCK) has been shown to counteract the analgesic effects of **morphine** suggesting a physiological antagonism between **opioid** and CCK neural systems. This has been definitely demonstrated in this study by co-administration of the CCK-B selective antagonist L-365,260 with RB 101, a systemically active inhibitor of peptidases, which fully protects the endogenous **opioids**, the enkephalins, from their inactivation. The naloxone reversible analgesic effects induced by RB 101 in the mouse hot-plate and rat tail-flick tests were strongly increased by low doses of L-365,260. These results could have important clinical applications by reducing the efficient dose of RB 101, which has recently been shown to be practically devoid of **morphine**-like **side-effects**.

L7 ANSWER 14 OF 38 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2004026597 EMBASE
TITLE: Cholecystokinin antagonists a new way to improve the analgesia from old analgesics?.
AUTHOR: McCleane G.
CORPORATE SOURCE: G. McCleane, Rampark Pain Centre, 2 Rampark, Dromore Road, Lurgan BT66 7JH, United Kingdom. gary@mccleane.freeserve.co.uk
SOURCE: Current Pharmaceutical Design, (2004) 10/3 (303-314). Refs: 106 ISSN: 1381-6128 CODEN: CPDEFP
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Cholecystokinin, originally thought to be confined only to the gastrointestinal tract, is now known to be co-localised in both the gastrointestinal tract and central nervous system. In animal models levels are increased after neural injury and with **opioid** administration. This peptide acts as an anti-**opioid**, and as levels increase, the extent of **opioid** derived antinociception decreases. Co-administration of a CCK antagonist along with an **opioid** is associated with an improved level of antinociception. Furthermore CCK antagonists may prevent antinociceptive tolerance with **opioids** and even reverse established tolerance Human studies have now confirmed the pro-analgesic effect of some CCK antagonists. Human investigation of the effect of CCK antagonists on analgesic tolerance has yet to be performed. This review examines the available evidence that suggests a role for CCK antagonists in human pain management.

L7 ANSWER 15 OF 38 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2002439670 EMBASE
TITLE: Novel medical therapies for gastroesophageal reflux disease beyond proton-pump inhibitors.
AUTHOR: Richter J.E.
CORPORATE SOURCE: Dr. J.E. Richter, Department of Gastroenterology, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, United States
SOURCE: Gastroenterology Clinics of North America, (2002) 31/4 SUPPL. (S111-S116). Refs: 14 ISSN: 0889-8553 CODEN: GCNAEF
PUBLISHER IDENT.: S 0889-8553(02)00045-6
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 037 Drug Literature Index
038 Adverse Reactions Titles
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The control of TLESRs is a novel pharmacologic approach to the treatment of GERD. It is applicable in most reflux patients characterized as having nonerosive disease or patients with mild erosive disease. Currently, only the GABAB agonist baclofen is available for oral therapy, although **side effects** may be a limiting factor. Future drug development requires a better understanding of the central and peripheral mechanisms controlling TLESRs.

L7 ANSWER 11 OF 38 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 96362037 EMBASE
DOCUMENT NUMBER: 1996362037
TITLE: Association of enkephalin catabolism inhibitors and CCK-B antagonists: A potential use in the management of pain and **opioid** addiction.
AUTHOR: Roques B.P.; Noble F.
CORPORATE SOURCE: Dept. de Pharmacochimie Moleculaire, INSERM U266-CNRS URA D 1500, Universite Rene Descartes, 4, Avenue de l'Observatoire,75270 Paris Cedex 06, France
SOURCE: Neurochemical Research, (1996) 21/11 (1397-1410).
ISSN: 0364-3190 CODEN: NEREDZ
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The overlapping distribution of **opioid** and cholecystokinin (CCK) peptides and their receptors (μ and δ **opioid** receptors; CCK-A and CCK-B receptors) in the central nervous system have led to a large number of studies aimed at clarifying the functional relationships between these two neuropeptides. Most of the pharmacological studies devoted to the role of CCK and enkephalins have been focused on the control of pain. Recently the existence of regulatory mechanisms between both systems have been proposed, and the physiological antagonism between CCK and endogenous **opioid** systems has been definitely demonstrated by coadministration of CCK-B selective antagonists with RB 101, a systemically active inhibitor, which fully protects enkephalins from their degradation. Several studies have also been done to investigate the functional relationships between both systems in development of **opioid side-effects** and in behavioral responses. This article will review the experimental pharmacology of association of enkephalin- degrading enzyme inhibitors and CCK-B antagonists to demonstrate the interest of these molecules in the management of both pain and **opioid** addiction.

L7 ANSWER 12 OF 38 EMBASE COPYRIGHT

L7 ANSWER 9 OF 38 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:270788 CAPLUS
DOCUMENT NUMBER: 126:325409
TITLE: Antinociceptive effects of RB101, a complete inhibitor of enkephalin-catabolizing enzymes, are enhanced by a cholecystokinin type B receptor antagonist, as revealed by noxiously evoked spinal c-Fos expression in rats
AUTHOR(S): Honore, Prisca; Buritova, Jaroslava; Fournie-Zaluski, Marie-Claude; Roques, Bernard P.; Besson, Jean-Marie
CORPORATE SOURCE: Physiopharmacologie Systeme Nerveux, Inst. national Sante Recherche Medicale, Paris, 75014, Fr.
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1997), 281(1), 208-217
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of RB101, a complete inhibitor of enkephalin-catabolizing enzymes, alone or with a selective cholecystokinin (CCK)B receptor antagonist (CI988) or CCKA receptor antagonist (**devazepide**), on carrageenin-induced spinal c-Fos expression were investigated. Spinal c-Fos expression was observed 90 min after intraplantar carrageenin (6 mg/150 μl saline), with Fos-like-immunoreactive neurons preferentially located in the superficial laminae of the spinal dorsal horn. I.v. RB101 (10, 20 and 40 mg/kg) dose-dependently reduced the number of superficial Fos-like-immunoreactive neurons (r2=0.739), with 63% reduction for the highest dose. These effects were completely blocked by coadministered naloxone. Coadministration of inactive doses of i.v. RB101 (5 mg/kg) and i.p. CI988 (3 mg/kg) significantly and strongly reduced the number of carrageenin-induced, superficial, Fos-like-immunoreactive neurons (55% reduction of control carrageenin c-Fos expression). This effect was blocked by coadministered naloxone. It is important to note that coadministered RB101 and **devazepide** did not influence spinal c-Fos expression. None of the various drug combinations influenced the carrageenin-induced peripheral edema. These results show that RB101 dose-dependently decreases carrageenin-evoked spinal c-Fos expression. In addition, the effectiveness of RB101 can be revealed by preadministration of the CCKB receptor antagonist CI988. Considering the weak **opioid side effects** obtained with RB101 treatment and the strong increase of its effects by the CCKB receptor antagonist, this type of drug combination could have promising therapeutic application in the management of pain in humans.

REFERENCE COUNT: 81 THERE ARE 81 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 10 OF 38 USPATFULL on STN

L7 ANSWER 1 OF 38 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:825130 CAPLUS
TITLE: Method for the treatment of pain with **opioid** analgesics minimizing their **side effects** by administration of **devazepide**
INVENTOR(S): Gibson, Karen
PATENT ASSIGNEE(S): UK
SOURCE: U.S. Pat. Appl. Publ., 6 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004198723	A1	20041007	US 2002-53962	20020122
US 2003139396	A1	20030724	US 2002-108659	20020327
US 2003153592	A1	20030814	US 2003-349431	20030122
US 6713470	B2	20040330		
US 2004167146	A1	20040826	US 2003-622492	20030721
US 2004142959	A1	20040722	US 2004-752411	20040107

PRIORITY APPLN. INFO.:

GB 2002-1367	A	20020122
US 2002-53962	A2	20020122
US 2002-108659	A2	20020327
GB 2002-8129	A	20020409
US 2003-349431	A2	20030122

AB Method is disclosed for the treatment of a patient undergoing **opioid** analgesic therapy which comprises minimizing the **side effects** of the **opioid** by the administration of a therapeutically effective amount of **devazepide** .

L7 ANSWER 2 OF 38 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:633285 CAPLUS
DOCUMENT NUMBER: 139:159955
TITLE: Method and pharmaceutical composition using **devazepide** and surfactant with **opioid** analgesic therapy
INVENTOR(S): Jackson, Karen
PATENT ASSIGNEE(S): ML Laboratories PLC, UK
SOURCE: U.S. Pat. Appl. Publ., 8 pp., Cont.-in-part of U.S. Ser. No. 108,659.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003153592	A1	20030814	US 2003-349431	20030122
US 6713470	B2	20040330		
US 2004198723	A1	20041007	US 2002-53962	20020122
US 2003139396	A1	20030724	US 2002-108659	20020327
US 2004043990	A1	20040304	US 2003-410311	20030409
US 2004167146	A1	20040826	US 2003-622492	20030721
US 2004142959	A1	20040722	US 2004-752411	20040107

PRIORITY APPLN. INFO.:

US 2002-53962	B2	20020122
US 2002-108659	A2	20020327
GB 2002-1367	A	20020122
GB 2002-8129	A	20020409
US 2003-349431	A2	20030122

AB There is described a method of treatment of a patient requiring analgesia which comprises the sep., simultaneous or sequential administration of a therapeutically effective amount of an **opioid** analgesic, **devazepide** and a surfactant. There is also described a monophasic pharmaceutical composition comprising an amount of **devazepide** effective in the enhancement of **opioid** analgesia and a pharmaceutically acceptable surfactant. The use of a surfactant is advantageous in that it improves the powder flow and/or separation properties of solid **devazepide** and also reduces or mitigates the undesirable **side effects** of **opioid** administration, e.g. **constipation**.

L7 ANSWER 3 OF 38 USPATFULL on STN
ACCESSION NUMBER: 2004:185073 USPATFULL
TITLE: Method of treatment
INVENTOR(S): Jackson, Karen, Sheffield, UNITED KINGDOM

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004142959	A1	20040722
APPLICATION INFO.:	US 2004-752411	A1	20040107 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2003-349431, filed on 22 Jan 2003, GRANTED, Pat. No. US 6713470 Continuation-in-part of Ser. No. US 2002-108659, filed on 27 Mar 2002, PENDING Continuation-in-part of Ser. No. US 2002-53962, filed on 22 Jan 2002, ABANDONED

	NUMBER	DATE
PRIORITY INFORMATION:	GB 2002-1367	20020122

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: PATENT ADMINSTRATOR, KATTEN MUCHIN ZAVIS ROSENMAN, 525 WEST MONROE STREET, SUITE 1600, CHICAGO, IL, 60661-3693
NUMBER OF CLAIMS: 128
EXEMPLARY CLAIM: 1
LINE COUNT: 749
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB There is described a method of treatment of a patient requiring analgesia which comprises the separate, simultaneous or sequential administration of a therapeutically effective amount of an **opioid** analgesic, **devazepide** and a surfactant.

There is also described a monophasic pharmaceutical composition comprising an amount of **devazepide** effective in the enhancement of **opioid** analgesia and a pharmaceutically acceptable surfactant.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 4 OF 38 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:777598 CAPLUS
DOCUMENT NUMBER: 139:286355
TITLE: Use of **devazepide** for the treatment of **constipation**
INVENTOR(S): Jackson, Karen
PATENT ASSIGNEE(S): ML Laboratories PLC, UK
SOURCE: PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003080066	A1	20031002	WO 2003-GB1285	20030326

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2002-7091 A 20020326

AB There is described a method of treatment of a patient suffering from **constipation** characterized in that the method comprises the administration of an effective amount of **devazepide**. There is also described a method of treatment of a patient requiring analgesia which comprises the sep., simultaneous or sequential administration of a therapeutically effective amount of an analgesic and a laxative and/or stool softening amount of **devazepide**. The use of **devazepide** in the manufacture of a medicament is also described.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 5 OF 38 USPATFULL on STN

ACCESSION NUMBER: 2003:123105 USPATFULL

TITLE: Methods for manipulating upper gastrointestinal transit, blood flow, and satiety, and for treating visceral hyperalgesia

INVENTOR(S): Lin, Henry C., Manhattan Beach, CA, United States

PATENT ASSIGNEE(S): Cedars-Sinai Medical Center, Los Angeles, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6558708	B1	20030506
APPLICATION INFO.:	US 2000-546119		20000410 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1999-420046, filed on 18 Oct 1999 Continuation-in-part of Ser. No. US 1999-359583, filed on 22 Jul 1999, now abandoned Continuation of Ser. No. US 1997-832307, filed on 3 Apr 1997, now patented, Pat. No. US 5977175, issued on 2 Nov 1999 Continuation of Ser. No. US 1995-442843, filed on 17 May 1995, now abandoned

DOCUMENT TYPE: Utility

FILE SEGMENT: GRANTED

PRIMARY EXAMINER: Page, Thurman K.

ASSISTANT EXAMINER: Tran, S.

LEGAL REPRESENTATIVE: Sidley Austin Brown & Wood LLP

NUMBER OF CLAIMS: 13

EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 13 Drawing Figure(s); 6 Drawing Page(s)

LINE COUNT: 3377

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed are a method of manipulating the rate of upper gastrointestinal transit of a substance in a mammal. Also disclosed are methods of manipulating satiety and post-prandial visceral blood flow. A method of treating visceral pain or visceral hypersensitivity in a human subject is also described. A method for prolonging the residence time of an orally or enterally administered substance by promoting its dissolution, bioavailability and/or absorption in the small intestine is also described. These methods are related to a method of transmitting to

and replicating at a second location in the central nervous system a serotonergic neural signal originating at a first location in the proximal or distal gut of a mammal and/or a method of transmitting to and replicating at a second location in the upper gastrointestinal tract a serotonergic neural signal originating at a first location in the proximal or distal gut.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 6 OF 38 USPATFULL on STN

ACCESSION NUMBER:	2004:233760 USPATFULL		
TITLE:	Methods for manipulating upper gastrointestinal transit, blood flow, and satiety, and for treating visceral hyperalgesia		
INVENTOR(S):	Lin, Henry C., Manhattan Beach, CA, UNITED STATES		
PATENT ASSIGNEE(S):	Cedars-Sinai Medical Center (U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004180834	A1	20040916
APPLICATION INFO.:	US 2004-810020	A1	20040326 (10)
RELATED APPLN. INFO.:	Division of Ser. No. US 2001-837797, filed on 17 Apr 2001, PENDING Continuation-in-part of Ser. No. US 2000-546119, filed on 10 Apr 2000, GRANTED, Pat. No. US 6558708 Continuation-in-part of Ser. No. US 1999-420046, filed on 18 Oct 1999, ABANDONED Continuation-in-part of Ser. No. US 1999-359583, filed on 22 Jul 1999, ABANDONED Continuation of Ser. No. US 1997-832307, filed on 3 Apr 1997, GRANTED, Pat. No. US 5977175 Continuation of Ser. No. US 1995-442843, filed on 17 May 1995, ABANDONED		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	Intellectual Property Group, Pillsbury Winthrop LLP, Suite 2800, 725 South Figueroa Street, Los Angeles, CA, 90017-5406		
NUMBER OF CLAIMS:	12		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	6 Drawing Page(s)		
LINE COUNT:	2804		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed is a method of manipulating the rate of upper gastrointestinal transit of a substance in a mammal. Also disclosed are methods of manipulating satiety and post-prandial visceral blood flow. A method of treating visceral pain or visceral hypersensitivity in a human subject is also described. A method for prolonging the residence time of an orally or enterally administered substance by promoting its dissolution, bioavailability and/or absorption in the small intestine is also described. These methods are related to a method of transmitting to and replicating at a second location in the central nervous system a serotonergic neural signal originating at a first location in the proximal or distal gut of a mammal and/or a method of transmitting to and replicating at a second location in the upper gastrointestinal tract a serotonergic neural signal originating at a first location in the proximal or distal gut.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 7 OF 38 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER:	2003:570641 CAPLUS
DOCUMENT NUMBER:	139:111675
TITLE:	Method for **constipation** treatment
INVENTOR(S):	Gibson, Karen
PATENT ASSIGNEE(S):	UK

SOURCE: U.S. Pat. Appl. Publ., 4 pp., Cont.-in-part of U.S. Ser. No. 53,962.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003139396	A1	20030724	US 2002-108659	20020327
US 2004198723	A1	20041007	US 2002-53962	20020122
US 2003153592	A1	20030814	US 2003-349431	20030122
US 6713470	B2	20040330		
US 2004167146	A1	20040826	US 2003-622492	20030721
US 2004142959	A1	20040722	US 2004-752411	20040107

PRIORITY APPLN. INFO.:

US 2002-53962	A2	20020122
GB 2002-1367	A	20020122
US 2002-108659	A2	20020327
GB 2002-8129	A	20020409
US 2003-349431	A2	20030122

AB Method is disclosed for the treatment of a patient suffering from **constipation**. Method comprises the administration of a therapeutically effective amount of **devazepide**. There is also described a method of treatment of a patient requiring analgesia which comprises the sep., simultaneous or sequential administration of a therapeutically effective amount of an analgesic and a stool softening amount of **devazepide**. The use of **devazepide** in the manufacture of a medicament is also described.

L7 ANSWER 8 OF 38 MEDLINE on STN
ACCESSION NUMBER: 92204911 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1553366
TITLE: A pilot clinical trial of the cholecystokinin receptor antagonist **MK-329** in patients with advanced pancreatic cancer.
AUTHOR: Abbruzzese J L; Gholson C F; Daugherty K; Larson E; DuBrow R; Berlin R; Levin B
CORPORATE SOURCE: Department of Medical Oncology, University of Texas M. D. Anderson Cancer Center, Houston 77030.
SOURCE: Pancreas, (1992) 7 (2) 165-71.
Journal code: 8608542. ISSN: 0885-3177.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199204
ENTRY DATE: Entered STN: 19920509
Last Updated on STN: 19990129
Entered Medline: 19920428

AB **MK-329** is a nonpeptidal, highly specific cholecystokinin (CCK) receptor antagonist, with affinity for pancreatic and gallbladder CCK receptors similar to CCK itself. **MK-329** and its progenitor, asperlicin, can inhibit the growth of CCK receptor-positive human pancreatic cancer in athymic mice. Based on these activities and the ability of **MK-329** to transiently increase food intake and enhance **morphine** analgesia in murine models, we conducted an open trial of **MK-329** in 18 patients with advanced pancreatic cancer in whom the CCK receptor status of the tumors was unknown. Tumor response, pain control, and nutritional parameters (hunger rating, caloric intake, body weight, and anthropometrics) were serially assessed. The results of the study failed to demonstrate any impact of **MK-329** on tumor

progression, pain, or nutrition. Toxicity was mild and limited to **nausea**, vomiting, diarrhea, and abdominal cramps, with 17 of 18 patients able to tolerate treatment. While a role for **MK-329** in the management of patients with advanced pancreatic cancer cannot be supported by the results of this trial, additional studies of this agent in patients with known CCK receptor-positive tumors, at escalated doses, and possibly in conjunction with other growth antagonists, appear warranted.

L7 ANSWER 9 OF 38 CAPLUS COPYRIGHT 200

L5 ANSWER 46 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:125510 CAPLUS
DOCUMENT NUMBER: 120:125510
TITLE: The antagonistic effect of cholecystokinin octapeptide (CCK-8) on **opioid** effects in cardiovascular activities was mediated by CCK-B receptor
AUTHOR(S): Mei, Lin; Han, Jisheng
CORPORATE SOURCE: Dep. Physiol., Beijing Med. Univ., Beijing, 100083, Peop. Rep. China
SOURCE: Science in China, Series B: Chemistry, Life Sciences, & Earth Sciences (1993), 36(7), 817-23
CODEN: SCBSE5; ISSN: 1001-652X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Previous studies have shown that CCK-8 has distinct anti-**opioid** effect in the central sites related with pain control and blood pressure control. The aim of this study was to explore the receptor mechanism by which CCK-8 antagonized the depressor effect of μ- and κ-**opioid** agonists, and to observe whether CCK-8 could antagonize the depressor effect induced by muscimol, a nonopioid substance. The results showed that: (i) the antagonistic effect of CCK-8 on **opioid** -induced hypotension could be blocked by intrathecal administration of CCK-B antagonist L-365,260 at nanogram doses, or by CCK-A antagonist **devazepide** at doses 20-40 times higher than L-365,260, indicating that it was the CCK-B receptor which mediates the anti-**opioid** effect; (ii) the depressor effect induced by intrathecal muscimol, a GABA agonist, was blocked neither by naloxone nor by CCK-8, supporting the notion that CCK-8 is an endogenous **opioid** antagonist rather than a universal anti-hypotension agent.

L5 ANSWER 45 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:596448 CAPLUS
DOCUMENT NUMBER: 121:196448
TITLE: Cholecystokinin octapeptide (CCK-8) antagonizes **morphine** analgesia in nucleus accumbens of the rat via the CCK-B receptor
AUTHOR(S): Pu, Su-Fen; Zhuang, Hui-Xin; Han, Ji-Sheng
CORPORATE SOURCE: Neuroscience Research Center and, Beijing, 100083, Peop. Rep. China
SOURCE: Brain Research (1994), 657(1-2), 159-64
CODEN: BRREAP; ISSN: 0006-8993
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The analgesic effect of systemic **morphine** (4 mg/kg, s.c.) was antagonized in a dose-dependent manner by cholecystokinin octapeptide (CCK-8) (0.1-0.5 ng) administered bilaterally to the nucleus accumbens of the rat. This effect of CCK-8 could be reversed by **devazepide**, a CCK-A receptor antagonist, at 50 ng and 200 ng and by L-365,260, a CCK-B receptor antagonist, at 5 ng administered bilaterally to the nucleus accumbens. A marked potentiation of **morphine** analgesia was achieved by intra-nucleus accumbens injection of 200 ng **devazepide** or 5 ng L-365,260. Since the effect of L-365,260 in antagonizing the anti-**opioid** effect of CCK-8 in the nucleus accumbens is 40 times more potent than **devazepide**, it is suggested that the anti-**opioid** effect of CCK-8 is mediated by CCK-B receptors. In conclusion, nucleus accumbens is a strategic site where CCK-8 exerts an anti-**opioid** activity, most probably via the CCK-B receptors.

L5 ANSWER 44 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:81341 CAPLUS
DOCUMENT NUMBER: 132:189916
TITLE: Effects of spinal cholecystokinin receptor antagonists on **morphine** antinociception in a model of visceral pain in the rat
AUTHOR(S): Friedrich, Ann E.; Gebhart, Gerald F.
CORPORATE SOURCE: Department of Pharmacology, University of Iowa College of Medicine, Iowa City, IA, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2000), 292(2), 538-544
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The objective of the present study was to determine the effects of spinal cholecystokinin (CCK) receptor antagonists on **morphine** antinociception in a model of visceral nociception, colorectal distension, in rats with chronic colonic inflammation and vehicle-treated controls. Three to five days after intracolonic instillation of 2,4,6-trinitrobenzenesulfonic acid (TNBS), an enhanced visceromotor response to all pressures of colorectal distension (10-80 mm Hg) was evident. The ED50 of intrathecal **morphine** (0.93 μg) in vehicle-treated rats produced significantly greater antinociception in TNBS-treated rats. Intrathecal proglumide, a nonselective CCK receptor antagonist, dose dependently enhanced the antinociceptive effect of **morphine** in vehicle-treated rats, but not in TNBS-treated rats. Similarly, L-365260, a specific CCKB receptor antagonist, dose dependently increased **morphine**'s antinociceptive effects in vehicle-treated rats but had no effect in rats with TNBS-induced colonic inflammation. **L-364718**, a specific CCKA receptor antagonist, had no effect on **morphine** antinociception in either vehicle-treated or TNBS-treated rats. These data indicate that CCK, acting at the CCKB receptor, is involved in modulating **morphine** antinociception following a noxious visceral stimulus. However, CCK receptor antagonists no longer enhance **morphine** antinociception after instillation of intracolonic TNBS, suggesting that visceral inflammation may lead to a reduction in spinal CCK release.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 41 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:60728 CAPLUS
DOCUMENT NUMBER: 130:277059
TITLE: Effect of **devazepide** reversed antagonism of CCK-8 against **morphine** on electrical and mechanical activities of rat duodenum in vitro
AUTHOR(S): Xu, Man-Ying; Lu, Hui-Ming; Wang, Shu-Zhen; Shi, Wen-Yan; Wang, Xin-Chun; Yang, Dong-Xiao; Yang, Chun-Xiao; Yang, Li-Zhuang
CORPORATE SOURCE: Department of Physiology, Harbin Medical University, Harbin, 150086, Peop. Rep. China
SOURCE: World Journal of Gastroenterology (1998), 4(6), 524-526
CODEN: WJGAF2; ISSN: 1007-9327
PUBLISHER: World Journal of Gastroenterology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Studies were carried out to investigate the antagonism of cholecystokinin octapeptide (CCK-8) against effect of **morphine** and its mechanism. The elec. and mech. activities of rat duodenum in vitro were recorded simultaneously. Acetylcholine (ACh) could increase the amplitude and the number of the spike potential (SPA and SPN) of rat duodenum in vitro, followed by the increase of the duodenal contraction amplitudes (CA), showing a pos. correlation. **Morphine**, on the contrary, inhibited the potentiation of ACh, showing a neg. correlation. CCK-8 could antagonize the effects of **morphine**, i. e. SPA and SPN were increased again, followed by the increase of CA. CCK-A receptor antagonist **devazepide** could reverse the antagonism of CCK-8 to the effect of **morphine**. CCK-8 could antagonize the effect of **morphine** which inhibited the potentiation of ACh on the duodenal activities in vitro. The antagonistic effect of CCK-8 on **morphine** was mainly mediated by CCK-A receptor.
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 40 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:570641 CAPLUS
DOCUMENT NUMBER: 139:111675
TITLE: Method for constipation treatment
INVENTOR(S): Gibson, Karen
PATENT ASSIGNEE(S): UK
SOURCE: U.S. Pat. Appl. Publ., 4 pp., Cont.-in-part of U.S. Ser. No. 53,962.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003139396	A1	20030724	US 2002-108659	20020327
US 2004198723	A1	20041007	US 2002-53962	20020122
US 2003153592	A1	20030814	US 2003-349431	20030122
US 6713470	B2	20040330		
US 2004167146	A1	20040826	US 2003-622492	20030721
US 2004142959	A1	20040722	US 2004-752411	20040107

PRIORITY APPLN. INFO.:

US 2002-53962	A2	20020122
GB 2002-1367	A	20020122
US 2002-108659	A2	20020327
GB 2002-8129	A	20020409
US 2003-349431	A2	20030122

AB Method is disclosed for the treatment of a patient suffering from constipation. Method comprises the administration of a therapeutically effective amount of **devazepide**. There is also described a method of treatment of a patient requiring analgesia which comprises the sep., simultaneous or sequential administration of a therapeutically effective amount of an analgesic and a stool softening amount of **devazepide**. The use of **devazepide** in the manufacture of a medicament is also described.

L5 ANSWER 39 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:367018 CAPLUS
DOCUMENT NUMBER: 122:123633
TITLE: Cholecystokinin potentiates **morphine** anticonvulsant action through both CCK-A and CCK-B receptors
AUTHOR(S): Legido, A.; Adler, M. W.; Karkanias, C.; Geller, E. B.; Bradley, E.; Greenstein, J. I.; Grover, W. D.
CORPORATE SOURCE: Temple University School of Medicine, Philadelphia, PA, USA
SOURCE: Neuropeptides (Edinburgh) (1995), 28(2), 107-13
CODEN: NRPPDD; ISSN: 0143-4179
PUBLISHER: Churchill Livingstone
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Recent studies have suggested that cholecystokinin may have a role in modulating the effects of the endogenous **opioid** system in physiol. functions such as thermoregulation and pain control. However, the possible interaction of cholecystokinin and **morphine** in epileptogenesis is unknown. The authors studied the effect of s.c. **morphine** and intracerebroventricularly administered cholecystokinin octapeptide sulfate ester and receptor antagonists CCK-A (**MK 329**) and CCK-B (L 365,260) on seizures provoked by maximal electroshock in male Sprague-Dawley rats. Seizures were induced through electrode-gel-coated ear clip electrodes by a high voltage, high internal resistance constant current generator, 30 min after **morphine** administration and 10 min after cholecystokinin-8-SE, CCK-A and CCK-B infusion. **Morphine** decreased the length of the tonic component of the seizure and cholecystokinin potentiated this decrease. Cholecystokinin antagonists blocked the effects of both cholecystokinin and **morphine**. The results suggest that cholecystokinin acts as an endogenous agonist with **opioids** in the regulation of seizures susceptibility through both CCK-A and B receptors and may be responsible for part of the anticonvulsant action of **morphine**.

L5 ANSWER 38 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:182525 CAPLUS
DOCUMENT NUMBER: 140:210804
TITLE: Method of analgesic treatment with **devazepide**
INVENTOR(S): Jackson, Karen
PATENT ASSIGNEE(S): UK
SOURCE: U.S. Pat. Appl. Publ., 6 pp., Cont.-in-part of U.S. Ser. No. 349,431.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004043990	A1	20040304	US 2003-410311	20030409
US 2003153592	A1	20030814	US 2003-349431	20030122
US 6713470	B2	20040330		
PRIORITY APPLN. INFO.:			GB 2002-8129 A	20020409
			US 2003-349431 A2	20030122
			US 2002-53962 B2	20020122
			US 2002-108659 A2	20020327

AB There is described a method of treatment of a patient requiring analgesic therapy which comprises the administration of an analgesically effective amount of **devazepide**. There is also described the use of **devazepide** in the manufacture of an analgesically effective medicament. Ten of seventeen patients had long-term pain relief (5-26 wk) with **devazepide**. The patients had pain with a neuropathic element and were taking regular, stable doses of strong **opioids**.

L5 ANSWER 37 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:265895 CAPLUS
DOCUMENT NUMBER: 130:316627
TITLE: Analgesic composition containing a CCK antagonist and an **opioid**
INVENTOR(S): Iversen, Leslie Lars
PATENT ASSIGNEE(S): Panos Therapeutics Limited, UK
SOURCE: PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9918967	A1	19990422	WO 1998-GB3076	19981012
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9895475	A1	19990503	AU 1998-95475	19981012
EP 1023072	A1	20000802	EP 1998-949092	19981012
EP 1023072	B1	20021211		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001519396	T2	20011023	JP 2000-515602	19981012
AT 229337	E	20021215	AT 1998-949092	19981012
ES 2189252	T3	20030701	ES 1998-949092	19981012

PRIORITY APPLN. INFO.: GB 1997-21746 A 19971015
WO 1998-GB3076 W 19981012

AB Pharmaceutical formulations, particularly suitable for treating chronic and neuropathic pain comprise an **opioid**-potentiating amount of a cholecystokinin (CCK) antagonist and an analgesic amount of an **opioid** in a pharmaceutically acceptable biphasic carrier comprising an organic phase comprising a glyceride derivative and a hydrophilic phase. An i.v. emulsion contained L-740093 0.00025, **morphine** sulfate 0.10, phosphatidylcholine 0.024, Pluronic F68 0.0040 g, soy bean oil 0.4000 mL, and water q.s. 2 mL.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 35 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:989670 CAPLUS
DOCUMENT NUMBER: 124:76328
TITLE: Effects of cholecystokinin receptor agonist and antagonists on **morphine** dependence in mice
AUTHOR(S): Zarrindast, Mohammad-Reza; Malekzadeh, Anahita; Rezayat, Mehdi; Ghazi-Khansari, M.
CORPORATE SOURCE: Sch. Med., Tehran Univ. Med. Sci., Teheran, Iran
SOURCE: Pharmacology & Toxicology (Copenhagen) (1995), 77(6), 360-4
CODEN: PHTOEH; ISSN: 0901-9928
PUBLISHER: Munksgaard
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In the present study, the effect of cholecystokinin agonists and antagonists on dependence to **morphine** in mice has been investigated. Mice were treated s.c. with **morphine** (50, 50 and 75 mg;kg) three times daily for 2-4 days, and a last dose of **morphine** (50 mg/kg) was administered on day 3, 4 or 5. Withdrawal syndrome (jumping) was precipitated by naloxone (2.5, 5 and 10 mg/kg) which was administered i.p. 2 h after the last dose of **morphine**. To study the effects of cholecystokinin receptor agonists or antagonists, 10 injection of **morphine** (3 administrations each day) for dependence and a dose of 5 mg/kg of naloxone for withdrawal induction were employed. Cholecystokinin-8 (0.001-0.01 mg/kg), low doses of the cholecystokinin agonists caerulein (0.00001 and 0.0001 mg/kg) and, unsulfated cholecystokinin (but not high doses) as well as the antagonists **MK-329** (0.5-1 mg/kg) and L-365,260 (0.5-1 mg/kg) elicit reduction of the naloxone-induced jumping. The inhibition of jumping induced by caerulein was reduced with the selective cholecystokinin antagonists **MK-329** and L-365,260. It is concluded that cholecystokinin mechanism(s) may be involved in **morphine** dependence, that the agonists may act on a presynaptic receptors and that the antagonists may work on postsynaptic receptors.

L5 ANSWER 1 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1990:48583 CAPLUS
DOCUMENT NUMBER: 112:48583
TITLE: Differential effects of the CCK antagonist, **MK-329**, on analgesia induced by **morphine**, social conflict (**opioid**) and defeat experience (non-**opioid**) in male mice
AUTHOR(S): Hendrie, C. A.; Shepherd, J. K.; Rodgers, R. J.
CORPORATE SOURCE: Dep. Psychol., Univ. Bradford, Bradford, BD7 1DP, UK
SOURCE: Neuropharmacology (1989), 28(10), 1025-32
CODEN: NEPHBW; ISSN: 0028-3908
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of the potent and selective CCK antagonist, **MK-329**, on **morphine**- and environmentally-induced analgesia were examined in male mice. The results show that **MK-329** (0.005-0.1 mg/kg) was devoid of intrinsic analgetic activity on the mouse tail-flick assay and, over the dose range 0.01-0.5 mg/kg, was without significant effect upon nonopioid analgesia, induced by defeat experience. However, opposite effects of **MK-329** on analgesia induced by **morphine** and **opioid**-mediated social conflict analgesia were observed I.e., 0.05-0.01 mg/kg **MK-329** (but not smaller doses) enhanced, and modestly prolonged, the duration of analgesia induced by 5 mg/kg **morphine**. In direct contrast, 0.0001-0.5 mg/kg of the CCK antagonist very potently inhibited **opioid**-typical analgesia in mice exposed to intense conspecific attack. In the latter studies, a residual short-lasting analgesia in mice, treated with **MK-329**, was found to be resistant to naloxone (5 mg/kg), indicating its non-**opioid** nature and confirming the lack of effect of the CCK antagonist on **opioid**-independent analgesia. It is suggested that the variable effects of **MK-329** on **morphine**-induced and **opioid**-mediated social conflict analgesia may reflect differential, dose-dependent effects at CCK-B and CCK-A sites resp., a proposal consistent with the 500-fold potency difference observed between the two models.

L5 ANSWER 2 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1989:166111 CAPLUS
DOCUMENT NUMBER: 110:166111
TITLE: **Morphine**-induced analgesia in the rat paw pressure test is blocked by CCK and enhanced by the CCK antagonist **MK-329**
AUTHOR(S): O'Neill, M. F.; Dourish, C. T.; Iversen, S. D.
CORPORATE SOURCE: Neurosci. Res. Cent., Merck Sharp and Dohme Res. Lab., Harlow/Essex, CM20 2QR, UK
SOURCE: Neuropharmacology (1989), 28(3), 243-7
CODEN: NEPHBW; ISSN: 0028-3908
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of cholecystokinin octapeptide sulfated (CCK) and the potent CCK antagonist **MK-329** (L-364, 718) on analgesia induced by **morphine** in the paw pressure test in the rat were examined Both CCK (4-16 μg/kg) and **MK-329** (0.1-8.0 mg/kg) had no effect on thresholds for pain when given alone, whereas **morphine** (2-16 mg/kg) induced dose-dependent analgesia. Cholecystokinin (4-16 μg/kg) abolished the analgesia induced by 8 mg **morphine**/kg. In contrast, doses of 1 and 2 mg **MK-329**/kg enhanced the analgesia induced by 8 and 4 mg **morphine**/kg resp. The present data are consistent with previous reports that CCK blocks, and CCK antagonists enhance, **opiate**-induced analgesia in response to thermal pain stimuli. In addition, CCK/

PRIORITY INFORMATION:	GB 2002-1367 20020122
DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	PATENT ADMINSTRATOR, KATTEN MUCHIN ZAVIS ROSENMAN, 525 WEST MONROE STREET, SUITE 1600, CHICAGO, IL, 60661-3693
NUMBER OF CLAIMS:	128
EXEMPLARY CLAIM:	1
LINE COUNT:	749

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB There is described a method of treatment of a patient requiring analgesia which comprises the separate, simultaneous or sequential administration of a therapeutically effective amount of an **opioid** analgesic, **devazepide** and a surfactant.

There is also described a monophasic pharmaceutical composition comprising an amount of **devazepide** effective in the enhancement of **opioid** analgesia and a pharmaceutically acceptable surfactant.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 5 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER:	1988:198236 CAPLUS
DOCUMENT NUMBER:	108:198236
TITLE:	Enhancement of **morphine** analgesia and prevention of **morphine** tolerance in the rat by the cholecystokinin antagonist L-364,718
AUTHOR(S):	Dourish, Colin T.; Hawley, Diane; Iversen, Susan D.
CORPORATE SOURCE:	Neurosci. Res. Cent., Merck Sharp and Dohme Res. Lab., Harlow/Essex, CM20 2QR, UK
SOURCE:	European Journal of Pharmacology (1988), 147(3), 469-72 CODEN: EJPHAZ; ISSN: 0014-2999
DOCUMENT TYPE:	Journal
LANGUAGE:	English

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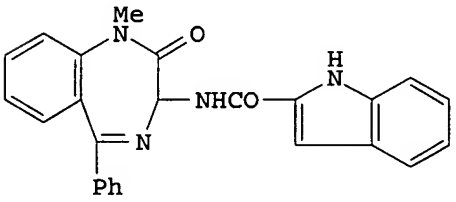

I

AB The potent and selective nonpeptide cholecystokinin (CCK) antagonist L-364,718 (I; 0.5-2.0 mg/kg s.c.) enhanced the analgesia induced by acute **morphine** treatment as evaluated by the tail-flick test in rats. Chronic treatment with 1.0 mg I/kg prevented the development of **morphine** tolerance during a 6-day **morphine** administration but did not influence the onset of **opioid** dependence. Since I is a considerably more potent inhibitor of CCK binding to peripheral tissues than to brain membranes, its interaction with **morphine** is surprising. The exact locus of this interaction and possible involvement of peripheral-type (CCK-A) or central-type (CCK-B) receptors is not known.

L5 ANSWER 6 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER:	1994:235987 CAPLUS
DOCUMENT NUMBER:	120:235987

TITLE: The CCKA receptor antagonist **devazepide** does not modify **opioid** self-administration or drug discrimination: comparison with the dopamine antagonist haloperidol
AUTHOR(S): Higgins, Guy. A.; Joharchi, Narges; Wang, Yephat; Corrigall, William A.; Sellers, Edward M.
CORPORATE SOURCE: Addiction Research Foundation and Departments of Pharmacology, Physiology and Medicine, University of Toronto, Toronto, Ont., Can.
SOURCE: Brain Research (1994), 640(1-2), 246-54
CODEN: BRREAP; ISSN: 0006-8993
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors previously reported that the selective cholecystokininA (CCKA) receptor antagonist, **devazepide**, blocked the acquisition of a **morphine** conditioned place preference. An interpretation of this finding is that **devazepide** may either affect an **opioid** discriminative stimulus and/or modify the rewarding properties of **opioids**. The present study was designed to investigate these issues by determining the effect of equivalent doses of **devazepide** in a **morphine** drug discrimination paradigm and a model of heroin self-administration. In each case, **devazepide** (0.001-1 mg/kg) was ineffective, i.e there was no antagonism of a **morphine** discriminative cue, and in a sep. group of rats trained to self-administer heroin (0.03 mg/kg/infusion, FR5 schedule, 1h per day), **devazepide** did not alter the pattern of heroin responding. Because of evidence implicating an interaction between accumbens CCK and dopamine (DA) systems and evidence suggesting an apparent differential involvement of DA in **opioid** place conditioning, self-administration and drug discrimination behavior, the effect of the DA antagonist haloperidol was examined in the latter two paradigms. In each test, haloperidol produced an effect inconsistent with a direct DAergic involvement. In a final study the CCKB antagonist L365-260 was also found not to affect an **opioid** discriminative cue. The present results therefore cast doubt on the potential utility of selective CCKA antagonists as treatments for **opioid** abuse, and further suggest that CCKB antagonists may not potentiate the subjective effects of **opioids**, an important finding considering that such drugs have been proposed as adjuncts to **opioid** therapy for the treatment of pain relief.

L5 ANSWER 7 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:633285 CAPLUS
DOCUMENT NUMBER: 139:159955
TITLE: Method and pharmaceutical composition using **devazepide** and surfactant with **opioid** analgesic therapy
INVENTOR(S): Jackson, Karen
PATENT ASSIGNEE(S): ML Laboratories PLC, UK
SOURCE: U.S. Pat. Appl. Publ., 8 pp., Cont.-in-part of U.S. Ser. No. 108,659.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003153592	A1	20030814	US 2003-349431	20030122
US 6713470	B2	20040330		
US 2004198723	A1	20041007	US 2002-53962	20020122
US 2003139396	A1	20030724	US 2002-108659	20020327
US 2004043990	A1	20040304	US 2003-410311	20030409
US 2004167146	A1	20040826	US 2003-622492	20030721

US 2004142959	A1	20040722	US 2004-752411	20040107
PRIORITY APPLN. INFO.:			US 2002-53962	B2 20020122
			US 2002-108659	A2 20020327
			GB 2002-1367	A 20020122
			GB 2002-8129	A 20020409
			US 2003-349431	A2 20030122

AB There is described a method of treatment of a patient requiring analgesia which comprises the sep., simultaneous or sequential administration of a therapeutically effective amount of an **opioid** analgesic, **devazepide** and a surfactant. There is also described a monophasic pharmaceutical composition comprising an amount of **devazepide** effective in the enhancement of **opioid** analgesia and a pharmaceutically acceptable surfactant. The use of a surfactant is advantageous in that it improves the powder flow and/or separation properties of solid **devazepide** and also reduces or mitigates the undesirable side effects of **opioid** administration, e.g. constipation.

L5 ANSWER 8 OF 166 USPATFULL on STN

ACCESSION NUMBER:	2003:123105 USPATFULL
TITLE:	Methods for manipulating upper gastrointestinal transit, blood flow, and satiety, and for treating visceral hyperalgesia
INVENTOR(S):	Lin, Henry C., Manhattan Beach, CA, United States
PATENT ASSIGNEE(S):	Cedars-Sinai Medical Center, Los Angeles, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6558708	B1	20030506
APPLICATION INFO.:	US 2000-546119		20000410 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1999-420046, filed on 18 Oct 1999 Continuation-in-part of Ser. No. US 1999-359583, filed on 22 Jul 1999, now abandoned Continuation of Ser. No. US 1997-832307, filed on 3 Apr 1997, now patented, Pat. No. US 5977175, issued on 2 Nov 1999 Continuation of Ser. No. US 1995-442843, filed on 17 May 1995, now abandoned

DOCUMENT TYPE:	Utility
FILE SEGMENT:	GRANTED
PRIMARY EXAMINER:	Page, Thurman K.
ASSISTANT EXAMINER:	Tran, S.
LEGAL REPRESENTATIVE:	Sidley Austin Brown & Wood LLP
NUMBER OF CLAIMS:	13
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	13 Drawing Figure(s); 6 Drawing Page(s)
LINE COUNT:	3377

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed are a method of manipulating the rate of upper gastrointestinal transit of a substance in a mammal. Also disclosed are methods of manipulating satiety and post-prandial visceral blood flow. A method of treating visceral pain or visceral hypersensitivity in a human subject is also described. A method for prolonging the residence time of an orally or enterally administered substance by promoting its dissolution, bioavailability and/or absorption in the small intestine is also described. These methods are related to a method of transmitting to and replicating at a second location in the central nervous system a serotonergic neural signal originating at a first location in the proximal or distal gut of a mammal and/or a method of transmitting to and replicating at a second location in the upper gastrointestinal tract a serotonergic neural signal originating at a first location in the proximal or distal gut.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 9 OF 166 USPATFULL on STN
ACCESSION NUMBER: 2004:233760 USPATFULL
TITLE: Methods for manipulating upper gastrointestinal transit, blood flow, and satiety, and for treating visceral hyperalgesia
INVENTOR(S): Lin, Henry C., Manhattan Beach, CA, UNITED STATES
PATENT ASSIGNEE(S): Cedars-Sinai Medical Center (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004180834	A1	20040916
APPLICATION INFO.:	US 2004-810020	A1	20040326 (10)

RELATED APPLN. INFO.: Division of Ser. No. US 2001-837797, filed on 17 Apr 2001, PENDING Continuation-in-part of Ser. No. US 2000-546119, filed on 10 Apr 2000, GRANTED, Pat. No. US 6558708 Continuation-in-part of Ser. No. US 1999-420046, filed on 18 Oct 1999, ABANDONED Continuation-in-part of Ser. No. US 1999-359583, filed on 22 Jul 1999, ABANDONED Continuation of Ser. No. US 1997-832307, filed on 3 Apr 1997, GRANTED, Pat. No. US 5977175 Continuation of Ser. No. US 1995-442843, filed on 17 May 1995, ABANDONED
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Intellectual Property Group, Pillsbury Winthrop LLP, Suite 2800, 725 South Figueroa Street, Los Angeles, CA, 90017-5406
NUMBER OF CLAIMS: 12
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 6 Drawing Page(s)
LINE COUNT: 2804
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Disclosed is a method of manipulating the rate of upper gastrointestinal transit of a substance in a mammal. Also disclosed are methods of manipulating satiety and post-prandial visceral blood flow. A method of treating visceral pain or visceral hypersensitivity in a human subject is also described. A method for prolonging the residence time of an orally or enterally administered substance by promoting its dissolution, bioavailability and/or absorption in the small intestine is also described. These methods are related to a method of transmitting to and replicating at a second location in the central nervous system a serotonergic neural signal originating at a first location in the proximal or distal gut of a mammal and/or a method of transmitting to and replicating at a second location in the upper gastrointestinal tract a serotonergic neural signal originating at a first location in the proximal or distal gut.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 10 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1991:464628 CAPLUS
DOCUMENT NUMBER: 115:64628
TITLE: Blockade of **morphine** place conditioning by the CCKA receptor antagonist **devazepide**
AUTHOR(S): Higgins, Guy A.; Nguyen, Peter; Sellers, Edward M.
CORPORATE SOURCE: Clin. Psychopharmacol. Program, Addict. Res. Found., Toronto, ON, M5S 2S1, Can.
SOURCE: European Journal of Pharmacology (1991), 197(2-3), 229-30
CODEN: EJPHAZ; ISSN: 0014-2999
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of **devazepide**, a CCKA receptor antagonist, and L365,260, a CCKB receptor antagonist, on the acquisition of

morphine place preference were studied in male Wistar rats. The results show that **devazepide** but not L365,260 blocked **morphine**-induced place preference. This suggests an involvement of CCKA receptors in the processes underlying **opioid** place conditioning which may be related to reward.

L5 ANSWER 11 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:105906 CAPLUS
DOCUMENT NUMBER: 130:276655
TITLE: Cholecystokinin receptor mechanism(s) and **morphine** tolerance in mice
AUTHOR(S): Zarrindast, Mohammad-Reza; Nikfar, Shekofeh; Rezayat, Mehdi
CORPORATE SOURCE: Department of Pharmacology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
SOURCE: Pharmacology & Toxicology (Copenhagen) (1999), 84(1), 46-50
CODEN: PHTOEH; ISSN: 0901-9928
PUBLISHER: Munksgaard International Publishers Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In a previous work, the effects of cholecystokinin receptor agonists on tolerance to **morphine** antinociception were evaluated. In the present study, the influence of cholecystokinin antagonists on the inhibition of tolerance to **morphine** antinociception by cholecystokinin agonists has been investigated. Maximum tolerance to **morphine** antinociception was obtained by **morphine** administration (50 mg/kg) to mice once daily for 4 days. The cholecystokinin receptor agonists caerulein (0.005 mg/kg) or cholecystokinin-8 (0.01 mg/kg) but not unsulfated cholecystokinin-8 (0.01 mg/kg) decreased the development of tolerance to **morphine** (9 mg/kg). The cholecystokininA receptor antagonist **MK-329** (1 mg/kg) or the cholecystokininB receptor antagonist L-365260 (0.25, 0.5 and 1 mg/kg) also diminished the tolerance to **morphine** antinociception. When animals were challenged with different doses of **MK-329** (0.25, 0.5 and 1 mg/kg) against cholecystokinin-8 (0.01 mg/kg), caerulein (0.05 mg/kg) or unsulfated cholecystokinin-8 (0.01 mg/kg) on day 4 in tolerant mice, different response were obtained. Higher doses of **MK-329** (1 mg/kg) caused a small decrease in attenuation of the **morphine** tolerance induced by cholecystokinin-8 and caerulein. Low doses of L-365260 diminished the effect of cholecystokinin-8 on **morphine** tolerance. Conversely high doses of the drug potentiated the response of caerulein (0.005 mg/kg). When animals were treated with **MK-329** or L-365260 before unsulfated cholecystokinin-8, reduction of the tolerance to **morphine** antinociception was obtained. These data indicate that both cholecystokinin receptors may modulate **morphine** tolerance.
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 12 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1993:617859 CAPLUS
DOCUMENT NUMBER: 119:217859
TITLE: Enhancement of **opiate** analgesia by **devazepide** in a baboon dolorimetry model
AUTHOR(S): Klein, Hilton; Jackson, Robert; McCormick, Gwendolyn; Montgomery, Tamara; Frankenfield, Dale; Pouch, Walter; Soper, Keith; Murray, Kathy
CORPORATE SOURCE: Merck Sharp and Dohme Res. Lab., West Point, PA, 19486, USA
SOURCE: Mult. Cholecystokinin Recept. CNS (1992), 529-36. Editor(s): Dourish, Colin T. Oxford Univ. Press: Oxford, UK.
CODEN: 59HNAW

DOCUMENT TYPE: Conference
LANGUAGE: English
AB Dental dolorimetry in the baboon showed that the CCK antagonist derazepide potentiated alfentanil analgesia by an interaction that does not involved neural pathways other than those related to pain.

L5 ANSWER 13 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1990:172160 CAPLUS
DOCUMENT NUMBER: 112:172160
TITLE: The selective CCK-B receptor antagonist L-365,260 enhances **morphine** analgesia and prevents **morphine** tolerance in the rat
AUTHOR(S): Dourish, C. T.; O'Neill, M. F.; Coughlan, J.; Kitchener, S. J.; Hawley, D.; Iversen, S. D.
CORPORATE SOURCE: Neurosci. Res. Cent., Merck Sharp and Dohme Res. Lab., Harlow/Essex, CM20 2QR, UK
SOURCE: European Journal of Pharmacology (1990), 176(1), 35-44
CODEN: EJPHAZ; ISSN: 0014-2999
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of the selective cholecystokinin A (CCK-A) antagonist L-365,031 and the selective CCK-B antagonist L-365,260 on **morphine** analgesia and **opiate** tolerance and dependence in rats were examined L-365,031 and L-365,260 had no effect on baseline pain thresholds in the radiant heat tail flick test but enhanced analgesia induced by a submaximal dose of **morphine** (4 mg/kg). Similarly, L-365,260 did not effect pain thresholds in the paw pressure test but enhanced **morphine** analgesia in this model. Rats injected twice daily for 6 days with incremental doses of **morphine** became tolerant to the analgesic effects of the drug. Twice daily injections of either 8 mg L-365,031/kg of 0.2 mg L-365,260/kg prevented the development of tolerance to **morphine** analgesia. In contrast, L-365,260 had no influence on the development of **opiate** dependence in these animals, as assessed by naloxone-precipitated withdrawal. The rank order of potency of non-peptide CCK antagonist for enhancing **morphine** analgesia is L-365,260 > **MK-329** > L-365,031. This rank order correlates well with the potency of the antagonists in blocking CCK-B receptors in rodents and suggests that CCK/**opiate** interactions in this species are mediated by CCK-B receptors.

L5 ANSWER 14 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1988:542415 CAPLUS
DOCUMENT NUMBER: 109:142415
TITLE: The novel CCK antagonist L364,718 abolishes caerulein- but potentiates **morphine**-induced antinociception
AUTHOR(S): Rattray, Marcus; Jordan, Christopher C.; De Belleroche, Jackie
CORPORATE SOURCE: Dep. Biochem., Charing Cross and Westminister Med. Sch., London, W6 8RF, UK
SOURCE: European Journal of Pharmacology (1988), 152(1-2), 163-6
CODEN: EJPHAZ; ISSN: 0014-2999
DOCUMENT TYPE: Journal
LANGUAGE: English
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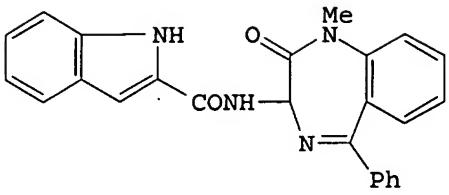


I

AB The novel cholecystokinin antagonist L364,718 (I) was tested on caerulein- and **morphine**-induced antinociception in rat using the paw pressure test. Caerulein-induced antinociception (ED50 = 30 μg/kg) was inhibited by L354,718 (200 μg/kg i.p.) which on its own did not affect paw pressure threshold. In contrast, **morphine**-induced antinociception as potentiated by L364,718. Since L364,718 is highly selective for peripheral cholecystokinin receptors, which are found in tissues such as pancreas and gallbladder and a few discrete areas of the brain, this receptor is likely to be implicated in the antinociceptive effect of caerulein.

L5 ANSWER 15 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:246265 CAPLUS
DOCUMENT NUMBER: 133:129756
TITLE: Cholecystokinin-B receptor antagonists attenuate **morphine** dependence and withdrawal in rats
AUTHOR(S): Lu, Lin; Huang, Mingsheng; Liu, Zhiyuan; Ma, Lan
CORPORATE SOURCE: Institute of Mental Health, West China University of Medical Sciences, Chengdu, Peop. Rep. China
SOURCE: NeuroReport (2000), 11(4), 829-832
CODEN: NERPEZ; ISSN: 0959-4965
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The possible effect of a cholecystokinin-8 agonist (caerulein) and antagonists (**MK-329** and L365,260) on the development of **morphine** dependence and withdrawal were investigated in rats. Caerulein treatment (0.01 and 0.1 mg/kg) increased the incidence of naloxone-induced withdrawal syndromes and delayed the extinction of **morphine**-conditioned place preference in **morphine** -dependent animals. The signs of the **morphine** withdrawal syndromes and the formation of **morphine**-conditioned place preference were suppressed by pretreatment with L365,260 (0.1 and 1 mg/kg) and not affected by pretreatment with **MK-329** (0.1 and 1 mg/kg). The present study demonstrated CCK, acting on CCK-B receptors, participates in the development of the **opiate** dependence. These findings suggest that CCK-B receptor antagonists might be of some value in the treatment and prevention the relapse of **opiate** addicts.
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

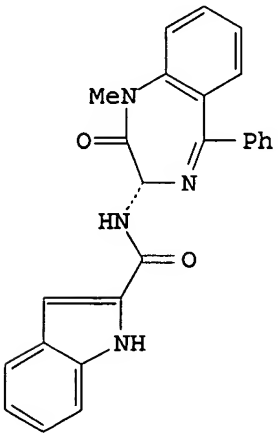
L5 ANSWER 16 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1992:187902 CAPLUS
DOCUMENT NUMBER: 116:187902
TITLE: The CCK-A and CCK-B receptor antagonists, **devazepide** and L-365,260, enhance **morphine** antinociception only in non-acclimated rats exposed to a novel environment
AUTHOR(S): Lavigne, G. J.; Millington, W. R.; Mueller, G. P.
CORPORATE SOURCE: Cent. Rech. Sci. Neurol., Univ. Montreal, Montreal, QC, Can.
SOURCE: Neuropeptides (Edinburgh, United Kingdom) (1992), 21(2), 119-29
CODEN: NRPPDD; ISSN: 0143-4179

DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Devazepide**, a potent CCK (cholecystokinin)-A receptor antagonist, and L-365,260, a selective CCK-B receptor antagonist, have been used as pharmacol. tools for differentiating the physiol. roles of CCK-A and CCK-B receptor subtypes. The present study tested the effects of **devazepide** and L-365,260 on **morphine**-induced antinociception in rats by means the thermal sensorimotor tail flick test. Both **devazepide** and L-365,260 enhanced the antinociceptive action of **morphine**, but only in rats that had not been acclimated to the laboratory environment or habituated to investigator handling.

When tested with fully acclimated animals, **devazepide** and L-365,260 had no effect whatsoever: they neither enhanced nor attenuated **morphine**-induced antinociception. Thus, the effects of **devazepide** and L-365,260, CCK antagonists, on **morphine** antinociception appear to be dependent on the animal's response to a new environment or to the stress induced by an unaccustomed exptl. paradigm.

L5 ANSWER 17 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1989:51173 CAPLUS
DOCUMENT NUMBER: 110:51173
TITLE: Blockade of CCK-induced hypophagia and prevention of **morphine** tolerance by the CCK antagonist L-364,718
AUTHOR(S): Dourish, Colin T.; Coughlan, Josephine; Hawley, Diane; Clark, Michael; Iversen, Susan D.
CORPORATE SOURCE: Neurosci. Res. Cent., Merck Sharp and Dohme Res. Lab., Harlow/Essex, CM20 2QR, UK
SOURCE: Neurology and Neurobiology (1988), 47(Cholecystokinin Antagonists), 307-25
CODEN: NEUND9; ISSN: 0736-4563
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB In rats, **L-364718** (I) produced a small increase in food intake, but reversed the increase in food intake induced by cholecystokinin (CCK), indicating that CCK may have a role in satiety. Also in rats, selective blockade of CCK receptors by I enhanced **morphine** analgesia by enhancing its peak effect and increasing the duration of analgesia. I also prevented the development of tolerance to **morphine** analgesia but did not influence the onset of dependence. These findings support the suggestion that CCK may act as an endogenous

opiate antagonist and inhibit the behavioral effects of **opiates**. Also, a CCK receptor antagonist such as I have therapeutic effects, possibly for use with **opiate** analgesia.

L5 ANSWER 18 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:141465 CAPLUS
DOCUMENT NUMBER: 131:28169
TITLE: Cholecystokinin and **morphine**-induced hypothermia
AUTHOR(S): Rezayat, Mehdi; Ravandeh, Neda; Zarrindast, Mohammad-Reza
CORPORATE SOURCE: School of Medicine, Department of Pharmacology, Tehran University of Medical Sciences, Tehran, Iran
SOURCE: European Neuropsychopharmacology (1999), 9(3), 219-225
CODEN: EURNE8; ISSN: 0924-977X
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of cholecystokinin-8 sulfate (CCK-8), cholecystokinin-8 unsulfate (CCK-8U), cholecystokinin-4 (CCK-4), caerulein and **morphine** on mice core body temperature have been studied in the present work. The s.c. injection of different doses of caerulein (0.05, 0.1 and 0.5 mg/kg), CCK-8 (0.05, 0.1 and 0.25 mg/kg) and **morphine** (10, 20 and 30 mg/kg) induced hypothermia. CCK-8U and CCK-4 did not elicit any response. The hypothermic response induced by caerulein, a CCK-related decapeptide but not **morphine** was decreased by selective CCKA receptor antagonist **MK-329**. However, the hypothermia induced by **morphine** but not caerulein was reduced by **opioid** antagonist naloxone. When **morphine** plus caerulein was administered a higher hypothermia was induced. Pretreatment of animals with L-365260, a selective CCKB receptor antagonist did not alter the hypothermia induced by the drugs. The response induced by combination of the both drugs was decreased by **MK-329**. Administration of CCK antagonists **MK-329** and L-365260 to mice did not exert any effect on temperature It is concluded that the CCKA receptor mechanism may be involved in the hypothermic effect of CCK agonists or **morphine**, while **opioid** receptor mechanism is not involved in CCK receptor agonists' response.
REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 19 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1993:400790 CAPLUS
DOCUMENT NUMBER: 119:790
TITLE: Increased release of immunoreactive cholecystokinin octapeptide by **morphine** and potentiation of μ- **opioid** analgesia by CCKB receptor antagonist L-365,260 in rat spinal cord
AUTHOR(S): Zhou, Yan; Sun, Yuhua; Zhang, Zhiwen; Han, Jishen
CORPORATE SOURCE: Neurosci. Res. Cent., Beijing Med. Univ., Beijing, 100083, Peop. Rep. China
SOURCE: European Journal of Pharmacology (1993), 234(2-3), 147-54
CODEN: EJPHAZ; ISSN: 0014-2999
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This is the first report showing, in an in vivo study, that systemic **morphine** produced a marked (89%, P<0.01) increase of the cholecystokinin octapeptide (CCK-8) immunoreactivity in the perfusate of the rat spinal cord, an effect completely reversed by naloxone. Since CCK-8 has been shown to possess potent anti-**opioid** activity at a spinal level, a blockade of the spinal cholecystokinin effect would be expected to potentiate **opiate** analgesia. With tail flick latency as a nociceptive index, it was found that intrathecal (i.t.)

injection of a novel CCKB antagonist L-365,260 produced a marked potentiation of the analgesic effect induced by the μ- **opioid** agonists **morphine** (4 mg/kg s.c.) or ohmefentanyl (32 ng i.t.). Similar effects were obtained with the CCKA antagonist **devazepide** at a dose 40-50 times higher than that of L-365,260. Both **devazepide** and L-365,260 showed a bell-shaped dose-response curve. The results confirm the notion that an increased release of CCK-8 may constitute of self-limiting process for **opioid** effects at the spinal level, and that it is the CCKB receptor which mediates the anti-**opioid** effect of CCK-8 in the rat spinal cord.

L5 ANSWER 20 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:825130 CAPLUS
TITLE: Method for the treatment of pain with **opioid** analgesics minimizing their side effects by administration of **devazepide**
INVENTOR(S): Gibson, Karen
PATENT ASSIGNEE(S): UK
SOURCE: U.S. Pat. Appl. Publ., 6 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004198723	A1	20041007	US 2002-53962	20020122
US 2003139396	A1	20030724	US 2002-108659	20020327
US 2003153592	A1	20030814	US 2003-349431	20030122
US 6713470	B2	20040330		
US 2004167146	A1	20040826	US 2003-622492	20030721
US 2004142959	A1	20040722	US 2004-752411	20040107
PRIORITY APPLN. INFO.:			GB 2002-1367 A	20020122
			US 2002-53962 A2	20020122
			US 2002-108659 A2	20020327
			GB 2002-8129 A	20020409
			US 2003-349431 A2	20030122

AB Method is disclosed for the treatment of a patient undergoing **opioid** analgesic therapy which comprises minimizing the side effects of the **opioid** by the administration of a therapeutically effective amount of **devazepide**.

L5 ANSWER 21 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:703123 CAPLUS
DOCUMENT NUMBER: 141:167833
TITLE: Method of analgesic treatment by administration of **devazepide**
INVENTOR(S): Jackson, Karen
PATENT ASSIGNEE(S): UK
SOURCE: U.S. Pat. Appl. Publ., 7 pp., Cont.-in-part of U.S. Ser. No. 349,431.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004167146	A1	20040826	US 2003-622492	20030721
US 2004198723	A1	20041007	US 2002-53962	20020122
US 2003139396	A1	20030724	US 2002-108659	20020327
US 2003153592	A1	20030814	US 2003-349431	20030122

US 6713470 B2 20040330

PRIORITY APPLN. INFO.:

US 2002-53962	B2 20020122
US 2002-108659	A2 20020327
GB 2002-8129	A 20020409
US 2003-349431	A2 20030122

AB A method of treating a patient undergoing analgesic therapy which comprises the sep., simultaneous or sequential administration of a therapeutically effective amount of an analgesic and an analgesic sparing amount of **devazepide**. There is also described the use of **devazepide** in the manufacture of a medicament which reduces the dose required for administration of an **opioid** analgesic and superpotentiates the effect of the analgesic.

L5 ANSWER 22 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1997:514990 CAPLUS

DOCUMENT NUMBER: 127:214998

TITLE: Effects of caerulein and CCK antagonists on tolerance induced to **morphine** antinociception in mice

AUTHOR(S): Zarrindast, Mohhamad-Reza; Zabihi, Ahmad; Rezayat, Mehdi; Rakhshandeh, Hasan; Ghazi-Khansari, Mahmoud; Hosseini, Rouhollah

CORPORATE SOURCE: Department of Pharmacology, School of Medicine and School of Pharmacy, Tehran University of Medical Sciences, Teheran, Iran

SOURCE: Pharmacology, Biochemistry and Behavior (1997), 58(1), 173-178
CODEN: PBBHAU; ISSN: 0091-3057

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Different groups of mice received one daily dose (50 mg/kg) of **morphine** s.c. (SC) for 3, 4 or 5 days to develop tolerance to the **opioid**. The antinociceptive response of **morphine** (9 mg/kg) was tested in the hot-plate test 24 h after the last dose of the drug. Tolerance to **morphine** was obtained in all groups. The group of mice that received **morphine** for 4 days was employed for the rest of the expts. Pretreatment of animals with a single dose of caerulein (0.025, 0.05, and 0.1 mg/kg, SC) 30 min prior to receiving **morphine** (50 mg/kg; during the development of tolerance to the **opioid**) on day 1,2,3,4 or 5 of **morphine** administration potentiate antinociception induced by **morphine** (test dose of 9 mg/kg). The dose of 0.05 mg/kg of caerulein, used 30 min before **morphine** administration on day 3, was also used to evaluate the effects of antagonists on caerulein-induced decrease in tolerance. The selective cholecystokinin (CCK) receptor antagonists, **MK-329** [1-methyl-3-(2 indoloyl)amino-5-phenyl-3H-1,4-benzodiazepin-2-one; 0.25 and 0.5 mg/kg] or I,-365,260 [3R(+)-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N-(3-methyl-phenyl)urea; 0.25 and 0 5 mg/kg] decreased potentiation of **morphine** response induced by caerulein. **MK-329** or L-365,260, when were injected 35 min before **morphine** injection during the development of tolerance and on day 3, decreased the tolerance to **morphine**. A single administration of **MK-329** or L-365,260 (in the absence of caerulein) 35 min and 48 h before the test dose of **morphine** (9 mg/kg) potentiated the antinociception of **morphine** in nontolerant animals. In conclusion, CCK mechanism(s) may interact with **morphine** tolerance.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 23 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:777598 CAPLUS

DOCUMENT NUMBER: 139:286355

TITLE: Use of **devazepide** for the treatment of

constipation
INVENTOR(S): Jackson, Karen
PATENT ASSIGNEE(S): ML Laboratories PLC, UK
SOURCE: PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003080066	A1	20031002	WO 2003-GB1285	20030326

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2002-7091 A 20020326

AB There is described a method of treatment of a patient suffering from constipation characterized in that the method comprises the administration of an effective amount of **devazepide**. There is also described a method of treatment of a patient requiring analgesia which comprises the sep., simultaneous or sequential administration of a therapeutically effective amount of an analgesic and a laxative and/or stool softening amount of **devazepide**. The use of **devazepide** in the manufacture of a medicament is also described.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 24 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:327254 CAPLUS
DOCUMENT NUMBER: 131:97825
TITLE: **Devazepide** reversed effect of sincalide against **morphine** on rat jejunal activities
AUTHOR(S): Xu, Man-Ying; Yang, Xin-Ping; Jin, Hong-Bo; Yang, Chun-Xiao; Yang, Li-Zhuang
CORPORATE SOURCE: Department of Physiology, Harbin Medical University, Harbin, 150086, Peop. Rep. China
SOURCE: Zhongguo Yaoli Xuebao (1999), 20(5), 419-422
CODEN: CYLPDN; ISSN: 0253-9756
PUBLISHER: Kexue Chubanshe
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To study the antagonism of sincalide to the effect of **morphine** and its mechanism, the electrophysiol. and mechanic activities of rat jejunum in vitro were recorded. Acetylcholine (ACh, 150 nmol·L-1) increased the spike potential amplitude (SPA) and the number (SPN) of rat jejunum in vitro, followed by an increase of jejunal contraction amplitudes (CA), showing a pos. correlation. **Morphine** (330 nmol·L-1) inhibited the potentiation of ACh, showing a neg. correlation. Sincalide (0.7 nmol·L-1) antagonized the effects of **morphine**, i.e., the SPA and SPN were increased again, followed by an increase of CA. CCK-A receptor antagonist **devazepide** (10 nmol·L-1) reversed the antagonism of sincalide to the effect of **morphine**. Sincalide antagonized the effect of **morphine** which inhibited the potentiation of ACh on jejunal activities in vitro. The antagonistic effect of sincalide on **morphine** was mainly

mediated by CCK-A receptor.
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 25 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:836862 CAPLUS
DOCUMENT NUMBER: 139:302070
TITLE: The use of **devazepide** as analgesic agent
INVENTOR(S): Jackson, Karen
PATENT ASSIGNEE(S): Ml Laboratories PLC, UK
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003086409	A1	20031023	WO 2003-GB1514	20030409

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2002-8129 A 20020409
AB There is described a method of treatment of a patient requiring analgesic therapy which comprises the administration of an analgesically effective amount of **devazepide**. There is also described the use of **devazepide** in the manufacture of an analgesically effective medicament.
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 26 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:729935 CAPLUS
DOCUMENT NUMBER: 128:30569
TITLE: Cholecystokinin inhibits peripheral **opioid** analgesia in inflamed tissue
AUTHOR(S): Schafer, M.; Zhou, L.; Stein, C.
CORPORATE SOURCE: Behavioral Pharmacology and Genetics Section, Division of Intramural Research, National Institute on Drug Abuse, Baltimore, MD, 21224, USA
SOURCE: Neuroscience (Oxford) (1997), Volume Date 1998, 82(2), 603-611
CODEN: NRSCDN; ISSN: 0306-4522
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB There is abundant evidence that **opioid** receptors are present on peripheral terminals of primary afferent neurons. Exptl. and clin. studies have shown that activation of these peripheral **opioid** receptors produces potent analgesia. In addition to peripheral **opioid** receptors, cholecystokinin receptors are present in sensory neurons. The authors examined the hypothesis that cholecystokinin receptors may be present on the same primary afferent neuron and that either exogenous or endogenous cholecystokinin may modulate peripheral antinociceptive effects of μ- **opioid** receptor agonists. Administration of cholecystokinin into inflamed paws, of the rat, but not

i.v. attenuated peripheral antinociceptive effects induced by two μ-**opioid** receptor agonists, [D-Ala2,N-methyl-Phe4,Gly-ol5]-enkephalin and fentanyl. Only the desulfated form of cholecystokinin produced significant and dose-dependent attenuation. Cholecystokinin alone did not alter nociceptive baseline values in inflamed or non-inflamed paws. The anti-**opioid** effect of cholecystokinin was dose-dependently antagonized by the cholecystokininB receptor-selective antagonist L-365260, but not by the cholecystokininA receptor-selective antagonist **L-364718**. Local pretreatment with the protein kinase C specific inhibitor calphostin C abolished cholecystokinin's effect. Peripheral antinociceptive effects of [D-Ala2,N-methyl-Phe4,Gly-ol5]-enkephalin and fentanyl were not altered by intraplantar L-365260 alone. These results indicate that activation of peripheral cholecystokininB but not cholecystokininA receptors attenuates the local antinociceptive effects of μ- **opioid** receptor agonists in inflamed tissue. This anti-**opioid** effect may be mediated by protein kinase C in sensory nerve terminals. Endogenous cholecystokinin does not seem to influence the efficacy of peripheral **opioids** under both normal and inflammatory conditions.

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 27 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:113192 CAPLUS
DOCUMENT NUMBER: 135:205338
TITLE: Different role of cholecystokinin (CCK)-A and CCK-B receptors in relapse to **morphine** dependence in rats
AUTHOR(S): Lu, L.; Huang, M.; Ma, L.; Li, J.
CORPORATE SOURCE: National Laboratory of Medical Neurobiology, Shanghai Medical University, Shanghai, 200032, Peop. Rep. China
SOURCE: Behavioural Brain Research (2001), 120(1), 105-110
CODEN: BBREDI; ISSN: 0166-4328
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The possible effects of different CCK receptor antagonists (**MK-329** and L-365260) on the maintenance and reactivation of **morphine** conditioned place preference (CPP) were investigated in rats. Maintenance of **morphine** CPP could be induced by injection of **morphine** (10 mg/kg, s.c.), and this effect was attenuated by pretreatment with 1 but not by 0.1 mg L-365260/kg. Furthermore, following a 28-day extinction, the **morphine** CPP disappeared and then was reactivated again by a single injection of **morphine** (10 mg/kg). Pretreatment with L-365260 (1 and 0.1 mg/kg) blocked this reactivation of **morphine** CPP. In contrast, pretreatment with **MK-329** (1 and 0.1 mg/kg) failed to do so. Thus, CCK-B receptors but not CCK-A receptors are involved in the maintenance and reactivation of **morphine** CPP. These findings suggest that CCK-B receptor antagonists might be of value in the treatment and prevention of relapse to drug dependence long after detoxification.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 28 OF 166 USPATFULL on STN
ACCESSION NUMBER: 2004:123062 USPATFULL
TITLE: Control of cancer growth through the interaction of [MET5]-enkephalin and the zeta receptor
INVENTOR(S): Zagon, Ian S., Hummelstown, PA, United States
McLaughlin, Patricia J., Harrisburg, PA, United States
Smith, Jill P., Camp Hill, PA, United States
PATENT ASSIGNEE(S): The Penn State Research Foundation, University Park, PA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6737397	B1	20040518
APPLICATION INFO.:	US 2000-640622		20000817 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1997-827841, filed on 27 Mar 1997, now patented, Pat. No. US 6136780

	NUMBER	DATE
PRIORITY INFORMATION:	US 1996-15193P	19960329 (60)
	US 1996-25922P	19960911 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Caputa, Anthony C.
ASSISTANT EXAMINER: Davis, Minh Tam
LEGAL REPRESENTATIVE: Scully, Scott, Murphy & Presser
NUMBER OF CLAIMS: 5
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 39 Drawing Figure(s); 25 Drawing Page(s)
LINE COUNT: 1791
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention is related to the treatment and prevention of cancer including particularly gastrointestinal cancer. More specifically, the present invention describes the use of naltrexone, naloxone and the pentapeptide growth factor [Met.sup.5]-enkephalin to inhibit and arrest the growth of cancer. Such efficiency has been discovered to be a consequence of the functional manipulation of the zeta (ζ) **opioid** receptor through endogenous [Met.sup.5]-enkephalin. This receptor has been determined to be present in growing cancers such as pancreatic and colon cancer, for example.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 29 OF 166 USPATFULL on STN
ACCESSION NUMBER: 2000:142347 USPATFULL
TITLE: Control of cancer growth through the interaction of [Met.sup.5]-enkephalin and the zeta (ζ) receptor
INVENTOR(S): Zagon, Ian S., Hummelstown, PA, United States
McLaughlin, Patricia J., Harrisburg, PA, United States
PATENT ASSIGNEE(S): The Penn State Research Foundation, University Park, PA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6136780		20001024
APPLICATION INFO.:	US 1997-827481		19970327 (8)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Ungar, Susan
ASSISTANT EXAMINER: Davis, Minh Tam
LEGAL REPRESENTATIVE: Monahan, Thomas J.
NUMBER OF CLAIMS: 14
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 39 Drawing Figure(s); 25 Drawing Page(s)
LINE COUNT: 1928
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention is related to the treatment and prevention of cancer including particularly gastrointestinal cancer. More specifically, the present invention describes the use of naltrexone, naloxone and the pentapeptide growth factor [Met.sup.5]-enkephalin to inhibit and arrest the growth of cancer. Such efficiency has been discovered to be a consequence of the functional manipulation of the zeta (ζ) **opioid** receptor through endogenous [Met.sup.5]-enkephalin. This receptor has been determined to be present in growing

cancers such as pancreatic and colon cancer, for example.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 30 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:95415 CAPLUS
DOCUMENT NUMBER: 120:95415
TITLE: Potentiation of **morphine**- and ohmefentanyl-induced analgesia by cholecystokinin receptor antagonists in rat
AUTHOR(S): Zhou, Yan; Sun, Yuhua; Han, Jisheng
CORPORATE SOURCE: Neurosci. Res. Cent., Beijing Med. Univ., Beijing, 100083, Peop. Rep. China
SOURCE: Shengli Xuebao (1993), 45(3), 255-61
CODEN: SLHPAH; ISSN: 0371-0874
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
AB It has been reported that intrathecal (i. t.) injection of CCK-8 showed a marked antagonism to analgesic effect mediated by μ- **opioid** receptors in rat. The present study was performed to ascertain whether the blockade of endogenously released CCK-8 by potent and selective CCK-A antagonist **devazepide** and CCK-B antagonist L-365260 would affect **opioid** analgesia at the spinal cord level. A marked potentiation of the analgesic effect induced by **morphine** (4 mg/kg, s.c.) was produced by i. t. injection of 100 ng **devazepide** or 2.5 ng L-365260. Dose-response curves for the enhancement of the two drugs on **morphine** analgesia were bell-shaped. Intrathecal injection of 66 ng **devazepide** or 1.25 ng L-365260 was also shown to potentiate the analgesic effect induced by the selective μ- **opioid** agonist ohmefentanyl (32 ng, i. t.). The dose-response curves were also bell-shaped. **Devazepide** or L-365260 per se produced no significant changes in rat tail flick latency. Thus, endogenously released CCK-8 in the spinal cord plays an antagonistic role in **opioid** analgesia, and it is the CCK-8 receptors that mediate the anti-**opioid** effect since the dose of **devazepide** is 40-50 times higher than that of L-365260.

L5 ANSWER 31 OF 166 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 91321990 EMBASE
DOCUMENT NUMBER: 1991321990
TITLE: **Devazepide, L-364718, MK-329.**
SOURCE: Drugs of the Future, (1991) 16/9 (853-856).
ISSN: 0377-8282 CODEN: DRFUD4
COUNTRY: Spain
DOCUMENT TYPE: Journal; (Short Survey)
FILE SEGMENT: 048 Gastroenterology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English

L5 ANSWER 32 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:273635 CAPLUS
DOCUMENT NUMBER: 122:47017
TITLE: Role of endogenous cholecystokinin in the facilitation of mu-mediated antinociception by delta-**opioid** agonists
AUTHOR(S): Noble, Florence; Smadja, Claire; Roques, Bernard P.
CORPORATE SOURCE: Dep. Pharm., Moleculaire Structurale, Universite Rene Descartes, Paris, 75270, Fr.
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1994), 271(3), 1127-34
CODEN: JPETAB; ISSN: 0022-3565

PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Published results suggest that delta-**opioid** agonists can modulate the mu-mediated analgesia. In this work, the antinociceptive effects produced by the mu agonist [D-Ala2,NMe-Phe4,Glyol5]enkephalin (DAMGO) or the mixed inhibitor of enkephalin-degrading enzymes RB 101 {N-[(R,S)-2-benzyl-3[(S)(2-amino-4-methylthio)butyldithio]-1-oxopropyl]-L-phenylalanine benzyl ester} were studied after administration of the systemically active and selective delta agonist Tyr-D-Ser(O-tert-butyl)-Gly-Phe-Leu-Thr(O-tert-butyl) (BUBU). In the hot-plate test in mice, BUBU (i.v.) potentiated the antinociceptive responses elicited by DAMGO (i.v.) or RB 101 (i.v.). These facilitatory effects were reversed not only by prior administration of the delta selective antagonist naltrindole (0.5 mg/kg, s.c.), but also unexpectedly by the selective cholecystokinin CCK-A antagonist **MK-329** (20 μg/kg, i.p.). In addition, the CCK analog [Boc-Tyr(SO3H)-Nle-Gly-Trp-Nle-Asp-Phe-NH2](BDNL) (a mixed CCK-A/CCK-B agonist) increased the jump latency, and this effect was blocked by **MK-329** (20 μg/kg, i.p.) and by naloxone, but not by the selective CCK-B antagonist L-365,260 (5 mg/kg, i.p.). In contrast, the selective CCK-B agonist BC 264 (62 μg/kg, i.v.) produced a hyperalgesic effect that was antagonized by L-365,260 (5 mg/kg, i.p.). Taken together, these findings suggest that the potentiating effects of delta agonists on mu-mediated analgesia are due to an increase in the release of endogenous CCK interacting with CCK-A and CCK-B receptors and resulting in pos. and neg. regulation of the endogenous **opioid** system. Under our exptl. conditions, the CCK-A agonist activity of endogenous CCK seems to be greater than its CCK-B activity, thus facilitating **opioid** analgesia.

L5 ANSWER 33 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:590987 CAPLUS
DOCUMENT NUMBER: 139:138761
TITLE: Method of treatment of patients requiring analgesia with **opioid** analgesics
INVENTOR(S): Jackson, Karen
PATENT ASSIGNEE(S): Ml Laboratories Plc, UK
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003061632	A1	20030731	WO 2003-GB221	20030122

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2002-1367 A 20020122

AB There is described a method of treatment of a patient requiring analgesia which comprises the sep., simultaneous or sequential administration of a therapeutically effective amount of an **opioid** analgesic, **devazepide**, and a surfactant. There is also described a monophasic pharmaceutical composition comprising **devazepide** effective

in the enhancement of **opioid** analgesia and a surfactant. The daily dosage of **devazepide** is up to 0.7 mg/kg/day.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 34 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1991:157138 CAPLUS
DOCUMENT NUMBER: 114:157138
TITLE: Influence of the selective cholecystokinin antagonist L-364,718 on pain threshold and **morphine** analgesia
AUTHOR(S): Poggioli, Rosanna; Vergoni, Anna Valeria; Sandrini, M.; Barbafiera, Lucia; Marrama, Donatella; Bertolini, A.
CORPORATE SOURCE: Inst. Pharmacol., Univ. Modena, Modena, I-41100, Italy
SOURCE: Pharmacology (1991), 42(4), 197-201
CODEN: PHMGBN; ISSN: 0031-7012
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Intracerebroventricular injections of the cholecystokinin A receptor antagonist L-364,718 at 0.5, 5, 10, or 20 μg/mouse, while having no effect on pain threshold (hot plate, 51°), antagonized the analgesic activity of **morphine** (10 mg/kg, i.p.). This effect was obtained with a dose of 10 μg/mouse and was associated with a reduction of brainstem **opiate**-binding sites.

L5 ANSWER 50 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:183533 CAPLUS
DOCUMENT NUMBER: 120:183533
TITLE: Characterization of SNF 9007, a novel cholecystokinin/**opioid** ligand in mouse ileum in vitro: evidence for involvement of cholecystokininA and cholecystokininB receptors in regulation of ion transport
AUTHOR(S): Rao, R. K.; Levenson, S.; Fang, S. N.; Hruby, V. J.; Yamamura, H. I.; Porreca, F.
CORPORATE SOURCE: Dep. Pharmacol., Univ. Arizona, Tucson, AZ, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1994), 268(2), 1003-9
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of cholecystokinin (CCK) fragments and Asp-Tyr-D-Phe-Gly-Trp-[N-Me]Nle-Asp-Phe-NH2 (SNF 9007), a synthetic CCK analog which binds with high affinity to CCKB and **opioid** delta receptors, were evaluated in isolated sheets of mouse ileum mounted in Ussing flux chambers. Serosal, but not mucosal, administration of cholecystokinin octapeptide-sulfated [CCK8(s)] and cholecystokinin tetrapeptide (30-33) [CCK4(30-33)] produced a brief, concentration-related increase in short circuit current (Isc) without changing tissue conductance. Serosal, but not mucosal, SNF 9007 produced a similar concentration-related increase in Isc which was followed by an immediate concentration-related and sustained decrease in Isc; no decrease in Isc was observed for either CCK8 or CCK4(30-33). The increase and subsequent decrease in the SNF 9007 Isc response were resp. classified as phase I (i.e., CCK-like) and phase II (**opioid**-like) activity. CCK8(s) and SNF 9007 (phase I) were active at low nanomolar concns., whereas CCK4(30-33) was active only at high nanomolar concns.: the rank order of potencies to increase Isc was CCK8(s) > SNF 9007 > CCK4(30-33). **Devazepide** (L364,718), a selective antagonist of CCKA receptors, effectively blocked the action of CCK8(s), but not that of CCK4(30-33) or SNF 9007 (phase I). In contrast, L365,260, a selective CCKB receptor antagonist, blocked the action of CCK4(30-33) and SNF 9007 (phase I), and also antagonized CCK8(s), though to a lesser degree. The phase II response of SNF 9007 was antagonized by N,N-diallyl-Tyr-Aib-Aib-Phe-Leu-OH (ICI 174,864), a selective **opioid** delta receptor antagonist; this **opioid** antagonist did not influence the phase I response. Neither L364,718 or L365,260 influenced the SNF 9007 phase II response. Serosal pretreatment of tissues with tetrodotoxin, or the ganglionic blocker chlorisondamine, significantly blocked the actions of CCK8(s) and CCK4(30-33), and both phase I and phase II responses to SNF 9007. Further, these peptides produced no significant response in mucosal prepns. of ileum phys. stripped of the enteric ganglia and muscularis externa. The data suggest that ileal ion-transport can be modulated by the activation of neural CCKA or CCKB receptors which are located partly preganglionically and that these receptors can be selectively activated by derivs. or analogs of CCK. CCK8(s) appears to produce its effects predominately, but not exclusively, at the CCKA receptor, whereas SNF 9007 and CCK4(30-33) selectively activate CCKB receptors in mouse ileum; SNF 9007 (phase I) is several-fold more potent than CCK4(30-33) in influencing ion transport at the CCKB receptor. Finally, SNF 9007 has the unusual profile of acting at **opioid** delta receptors to produce a subsequent decrease in Isc. These data demonstrate the importance of both CCKAa and CCKB, as well as **opioid** delta, receptors in the regulation of ion transport in the same intestinal segment.

=> d ibib abs 51-100 l5

L5 ANSWER 51 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:45454 CAPLUS
DOCUMENT NUMBER: 130:306407
TITLE: Cholecystokinin receptor agonists block the jumping behavior precipitated in **morphine**-dependent mice by naloxone
AUTHOR(S): Bourin, Michel; Malinge, Myriam; Colombel, Marie Claude; Vasar, Eero
CORPORATE SOURCE: Department of Pharmacology, GIS Medicament, Faculty of Medicine, Nantes, 44035, Fr.
SOURCE: European Neuropsychopharmacology (1999), 9(1-2), 37-43
CODEN: EURNE8; ISSN: 0924-977X
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The aim of present study was to reveal the role of cholecystokinin (CCK) in the jumping behavior induced by the **opioid** antagonist naloxone (30 mg/kg) after the acute administration of **morphine** (200 mg/kg) in mice. Treatment with caerulein (0.01-1 μg/kg), a nonselective agonist of CCK receptors, induced a large reduction of jumping frequency without parallel suppression of locomotor activity. The CCKB receptor agonist CCK tetrapeptide (CCK-4, 0.125-32 mg/kg) caused the same effect, but it happened at much higher doses (above 0.5 mg/kg). **Devazepide** (1 μg/kg), a preferential CCKA receptor antagonist, completely reversed the action of caerulein (0.1 gmg/kg) and CCK-4 (2 mg/kg). A preferential CCKB receptor antagonists LY 288,513 at a high dose (4 mg/kg) blocked the action of CCK-4, but not that of caerulein. Acetorphan (16-128 mg/kg), an inhibitor of enkephalin metabolism, did not block naloxone-precipitated jumping behavior. However, the combination of subthreshold doses of caerulein (0.001 μg/kg) and CCK-4 (0.25 mg/kg) with acetorphan (64 mg/kg) potently antagonized the behavior induced by naloxone. In conclusion, the antagonism of CCK agonists against naloxone-precipitated jumping behavior is apparently mediated via the CCKA receptor subtype. The stimulation of CCKA receptors seems to increase the release of endogenous enkephalins.
REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 52 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:762894 CAPLUS
DOCUMENT NUMBER: 123:161265
TITLE: Interaction between CCK and **opioids** in the modulation of the rectocolonic inhibitory reflex in rats
AUTHOR(S): Gue, Michele; Del Rio, Chantal; Junien, Jean Louis; Bueno, Lionel
CORPORATE SOURCE: Dep. Pharmacology, Inst. National Recherche Agronomique, Toulouse, 31931, Fr.
SOURCE: American Journal of Physiology (1995), 269(2, Pt. 1), G240-G245
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of cholecystokinin octapeptide (CCK-8) as well as the involvement of **opioid** system were evaluated in rectal distension (RD)-induced colonic motor inhibition in rats. Rats were surgically prepared with electrodes implanted on the proximal colon, and a catheter was implanted in lateral ventricle of the brain. RD was performed by inflation (0.0-1.6 mL) of a balloon rectally inserted. 1.6 ML RD induced an inhibition of the colonic spike burst (3.1 ± 0.5 per 5 min vs. 8.1 ± 0.4 before RD). Intracerebroventricular but not i.v. injection of CCK-8 and A-71623 (50 and 100 ng/kg) reduced the RD-induced colonic motor

inhibition, whereas A-63387 was ineffective. PD-135,158 (10 μg/kg icv) suppressed the inhibitory reflex caused by RD. **Devazepide** (100 μg/kg icv) had no effect in this reflex function. **Devazepide** (1 μg/kg), naloxone (0.1 mg/kg), and nor-binaltorphimine (nor-BNI; 10 mg/kg) reversed the blocking effect of CCK-8, whereas PD-135,158 (0.1 μg/kg) and naltrindole (1 mg/kg) have no effect. In conclusion, CCK-8 acts on central alimentary cholecystokinin receptors to modulate the RD-induced inhibition of colonic motility through pathways involving activation of endogenous κ-receptors.

L5 ANSWER 53 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:98706 CAPLUS
DOCUMENT NUMBER: 130:277095
TITLE: Antagonistic effect of CCK-8 on **morphine** -inhibited electrical and contractile activities of rat jejunum in vitro
AUTHOR(S): Xu, Man-Ying; Yang, Dong-Xiao; Wang, Shu-Zhen; Jin, Hong-Bo; Zou, Xiang-Hui; Yang, Xin-Ping; Han, Ji-Sheng
CORPORATE SOURCE: Department of Physiology, Harbin Medical University, Harbin, 150086, Peop. Rep. China
SOURCE: Shengli Xuebao (1998), 50(4), 469-473
CODEN: SLHPAH; ISSN: 0371-0874
PUBLISHER: Kexue Chubanshe
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In the present investigation, antagonistic action of cholecystokinin octapeptide (CCK-8) against **morphine** on the elec. and contractile activity of rat jejunum in vitro was studied. The results showed that the potentiation of acetylcholine (ACh) on both the burst of spike and the contractility were inhibited by **morphine**, which could be completely antagonized by CCK-8. The CCK-8 effect, again, could be suppressed by CCK-A receptor antagonist **devazepide** (10 nmol/L), but partially by CCK-B receptor antagonist L-365, 260 at 10 nmol/L or completely at concentration of 30 nmol/L. The above results demonstrated that the antagonism of CCK-8 on **morphine** was mediated by both CCK-A and CCK-B receptors.
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 54 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1990:417799 CAPLUS
DOCUMENT NUMBER: 113:17799
TITLE: Cholecystokinin antagonists proglumide, lorglumide and benzotript, but not L-364,718, interact with brain **opioid** binding sites
AUTHOR(S): Gaudreau, P.; Lavigne, G. J.; Quirion, R.
CORPORATE SOURCE: Res. Cent., Notre-Dame Hosp., Montreal, QC, H2L 4MI, Can.
SOURCE: Neuropeptides (Edinburgh, United Kingdom) (1990), 16(1), 51-5
CODEN: NRPPDD; ISSN: 0143-4179
DOCUMENT TYPE: Journal
LANGUAGE: English
AB It has been reported that proglumide and L-367,718 potentiate **opioid**-induced antinociception. However, their mode of action in pain modulation is still not understood. To evaluate a possible interaction with **opioid** receptors, the affinities of the cholecystokinin (CCK) antagonists proglumide, lorglumide, benzotript, and L-367,718 on μ, δ, and κ binding sites were determined, using guinea pig brain crude synaptosome prepns. These affinities were compared to that of the central CCK binding site, using rat brain slide-mounted sections. At 100 μM, proglumide competed for 13 and 17% of μ and κ binding sites, but did not interact with δ and CCK sites. At this concentration, lorglumide reduced μ, δ, κ, and CCK

specific binding by 44, 69, 35, and 88%, whereas benzotript diminished it by 16, 13, 38, and 48%, resp. L-364,718 did not interact with **opioid** receptors (assay limit of solubility, 10 μM) but had a high affinity for CCK binding sites (IC50, 126 nM). The lack of selectivity of proglumide, lorglumide, and benzotript for CCK receptors suggests that their reported ability to potentiate **morphine** analgesia may be related to an interaction with **opioid** receptors.

L5 ANSWER 55 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1993:596187 CAPLUS
DOCUMENT NUMBER: 119:196187
TITLE: Cholecystokinin-A but not cholecystokinin-B receptor stimulation induces endogenous **opioid** -dependent antinociceptive effects in the hot plate test in mice
AUTHOR(S): Derrien, M.; Noble, F.; Maldonado, R.; Roques, B. P.
CORPORATE SOURCE: UFR Sci. Pharm. Biol., Univ. Rene Descartes, Paris, 75270, Fr.
SOURCE: Neuroscience Letters (1993), 160(2), 193-6
CODEN: NELED5; ISSN: 0304-3940
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of intracerebroventricular administration of the CCK analog, BDNL, and the selective CCK-B agonist, BC 264, were determined using the hot plate test in mice. BDNL (0.2 nmol and 0.5 nmol) increased the jump and the paw lick latencies. These effects were blocked by the CCK-A antagonist **MK 329** (0.02 mg/kg), supporting the involvement of CCK-A receptors in CCK-induced analgesia. In contrast, the selective CCK-B agonist BC 264 produced, at 1 dose (2.5 nmol), a slight decrease in the lick latency that was only antagonized by the CCK-B antagonist. Naloxone, but not naltrindole, antagonized BDNL-induced analgesia. Apparently, activation of CCK-A receptors by BDNL leads to antinociceptive responses indirectly mediated by stimulation of μ-**opioid** receptors by endogenous enkephalins.

L5 ANSWER 56 OF 166 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 96343090 EMBASE
DOCUMENT NUMBER: 1996343090
TITLE: Opposite role of δ1- and δ2- **opioid** receptors activated by endogenous or exogenous **opioid** agonists on the endogenous cholecystokinin system: Further evidence for δ- **opioid** receptor heterogeneity.
AUTHOR: Noble F.; Fournie-Zaluski M.-C.; Roques B.P.
CORPORATE SOURCE: Dept. Pharmacochim. Mol./Structurale, INSERM U266, Universite Rene Descartes, 4 Avenue de l'Observatoire,75270 Paris Cedex 06, France
SOURCE: Neuroscience, (1996) 75/3 (917-926).
ISSN: 0306-4522 CODEN: NRSCDN
PUBLISHER IDENT.: S 0306-4522(96)00323-5
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
003 Endocrinology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Using the mouse caudate-putamen, where δ- **opioid** receptor subtypes have been shown to regulate adenylyl cyclase activity, we show in this study that endogenous enkephalins inhibit enzyme activity through activation of δ1- and δ2- **opioid** receptors. Thus, naltriben or 7-benzylidenenaltrexone as well as the δ-selective

antagonist naltrindole (mixed δ1 and δ2 antagonist) antagonized inhibition of adenylyl cyclase activity induced by methionine- or leucine-enkephalin, while the μ-antagonist D-Phe-Cys-Tyr-D-Trp-Orn-Thr-Pen-Thr-NH2 (CTOP) was without effect. Furthermore, we have previously shown that activation of δ- **opioid** receptors increases cholecystokinin release in the central nervous system, resulting in a potentiation of μ- **opioid** antinociceptive responses, and the respective role of δ1 and δ2- **opioid** receptors in this facilitatory effect has now been evaluated. Activation of δ2- **opioid** receptors, either by endogenous enkephalins protected from catabolism by the complete enkephalin-degrading enzyme inhibitor N-((R,S)-2-benzyl-3((S)(2-amino-4-methyl-thio) butyldithio)-1-oxopropyl)-L-phenyl-alanine benzyl ester (RB 101), or by the δ2-selective agonist Tyr-D-Ser(O-tert-butyl)-Gly-Phe-Leu-Thr(O-tert-butyl) (BUBU), potentiated μ- **opioid** antinociceptive responses in the hot-plate test in mice. This effect was antagonized by a selective cholecystokinin-A antagonist. Activation of δ1- **opioid** receptors by endogenous **opioid** peptides decreased the μ- **opioid** responses. These results suggest that stimulation of δ2- **opioid** receptors potentiates μ- **opioid** analgesia in the hot-plate test in mice through an increase in endogenous cholecystokinin release, while activation of δ1- **opioid** receptors could decrease it. Thus, the pre-existing physiological balance between **opioid** and cholecystokinin systems seems to be modulated in opposite directions depending on whether δ1- or δ2- **opioid** receptors are selectively activated. This is the first demonstration that endogenous enkephalins, methionine- and leucine-enkephalin, are the natural ligands of δ- **opioid** receptor subtypes, and that δ2- **opioid** receptor activation may facilitate the endogenous cholecystokinin-related modulation of μ- **opioid** analgesia, while the δ1- **opioid** receptors may have an inhibitory role. These results could have important applications for the characterization of **opioid** δ1 and δ2 as subtypes or subsites and in pain alleviation.

L5 ANSWER 57 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:717339 CAPLUS
DOCUMENT NUMBER: 137:352116
TITLE: Dietary peptides induce satiety via cholecystokinin-A and peripheral **opioid** receptors in rats
AUTHOR(S): Pupovac, Jelena; Anderson, G. Harvey
CORPORATE SOURCE: Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Toronto, ON, M5S 3E2, Can.
SOURCE: Journal of Nutrition (2002), 132(9), 2775-2780
CODEN: JONUAI; ISSN: 0022-3166
PUBLISHER: American Society for Nutritional Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The digestion of proteins gives rise to peptides that may initiate several satiety signals from the gut and these signals may be dependent on dietary protein sources. The role of peripheral **opioid** and cholecystokinin (CCK)-A receptors was investigated in male Wistar rats. Single doses of casein, soybean protein, casein hydrolyzate, and 3 com. soybean protein hydrolyzates were given to the rats by gavage at 0.5 g protein/4 mL water and subsequent feed intake was measured over 2 h. The **opioid** receptor antagonist naloxone methiodide (1.0 mg/kg i.p.) increased the feed intake when given at the same time as the hydrolyzate preloads, 25 min after the casein preloads, and 55 min after the soybean protein preloads. The CCK-A receptor antagonist **devazepide** (which reverses protein-induced feed intake suppression) given at 0.25 mg/kg i.p. 60 min before preloads of each of the 3 soybean hydrolyzates also blocked the suppression of feed intake, but the strength and duration of the interaction depended on the hydrolyzate preparation When the 2 receptor

antagonists were both given with soybean or casein preloads, their effects were additive. Thus, peptides arising from protein digestion contribute to satiety by independent activation of both **opioid** and CCK-A receptors.

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 58 OF 166 MEDLINE on STN
ACCESSION NUMBER: 92204911 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1553366
TITLE: A pilot clinical trial of the cholecystokinin receptor antagonist **MK-329** in patients with advanced pancreatic cancer.
AUTHOR: Abbruzzese J L; Gholson C F; Daugherty K; Larson E; DuBrow R; Berlin R; Levin B
CORPORATE SOURCE: Department of Medical Oncology, University of Texas M. D. Anderson Cancer Center, Houston 77030.
SOURCE: Pancreas, (1992) 7 (2) 165-71.
Journal code: 8608542. ISSN: 0885-3177.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199204
ENTRY DATE: Entered STN: 19920509
Last Updated on STN: 19990129
Entered Medline: 19920428

AB **MK-329** is a nonpeptidal, highly specific cholecystokinin (CCK) receptor antagonist, with affinity for pancreatic and gallbladder CCK receptors similar to CCK itself. **MK-329** and its progenitor, asperlicin, can inhibit the growth of CCK receptor-positive human pancreatic cancer in athymic mice. Based on these activities and the ability of **MK-329** to transiently increase food intake and enhance **morphine** analgesia in murine models, we conducted an open trial of **MK-329** in 18 patients with advanced pancreatic cancer in whom the CCK receptor status of the tumors was unknown. Tumor response, pain control, and nutritional parameters (hunger rating, caloric intake, body weight, and anthropometrics) were serially assessed. The results of the study failed to demonstrate any impact of **MK-329** on tumor progression, pain, or nutrition. Toxicity was mild and limited to nausea, vomiting, diarrhea, and abdominal cramps, with 17 of 18 patients able to tolerate treatment. While a role for **MK-329** in the management of patients with advanced pancreatic cancer cannot be supported by the results of this trial, additional studies of this agent in patients with known CCK receptor-positive tumors, at escalated doses, and possibly in conjunction with other growth antagonists, appear warranted.

L5 ANSWER 59 OF 166 MEDLINE on STN
ACCESSION NUMBER: 90137901 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2694075
TITLE: The role of CCK caerulein, and CCK antagonists in nociception.
AUTHOR: Baber N S; Dourish C T; Hill D R
CORPORATE SOURCE: Merck, Sharp and Dohme Research Laboratories, Harlow, Essex, U.K.
SOURCE: Pain, (1989 Dec) 39 (3) 307-28. Ref: 88
Journal code: 7508686. ISSN: 0304-3959.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 199003
ENTRY DATE: Entered STN: 19900328
Last Updated on STN: 19900328
Entered Medline: 19900309

AB The octapeptide form of CCK predominates in the central nervous system (CNS) of mammalian species, including man. Many of the physiological roles of CCK in the CNS are unknown, but it is believed to be involved in nociception. CCK is distributed throughout cortical grey matter, periaqueductal grey matter, ventromedial thalamus and spinal dorsal horn, all of which are areas known to be associated with pain modulation. CCK receptor subtypes have been identified and may be classified according to their affinity for the sulphated and desulphated forms of CCK-8 and the recently described selective antagonist. **MK-329**. CCK-A receptors have high affinity for sulphated CCK-8 and for **MK-329** but low affinity for desulphated CCK-8 and CCK-4 whilst CCK-B sites bind **MK-329** with low affinity and discriminate poorly between sulphated and desulphated CCK-8. CCK-A receptors are found predominantly in peripheral tissues but they also exist in discrete regions of the primate CNS, including the spinal cord. CCK-B receptors are found ubiquitously throughout other regions of the neuraxis. The results of studies on the effects of CCK-8 and the decapeptide analogue caerulein on pain thresholds are conflicting. Some workers suggest that large doses of CCK-8 and caerulein induce naloxone-reversible analgesia in certain pain models. However, it appears likely that analgesia induced by large doses of CCK and caerulein in animals may be a pharmacological rather than a physiological phenomenon. Accordingly, others have found that small (and most probably, physiological) doses of CCK-8 attenuate the analgesic effects of **morphine**, and of endogenous **opioids**. Thus, it has been proposed that CCK may act as an endogenous **opiate** antagonist. Studies in rats with the selective CCK antagonist **MK-329** have helped clarify the interaction between CCK and **morphine**-induced analgesia. Treatment with **MK-329** enhances **morphine** analgesia and chronic treatment with **MK-329** prevents the development of tolerance to **morphine** analgesia. However, the antagonist does not prevent naloxone-precipitated withdrawal symptoms in **morphine**-dependent rats. In man, caerulein prevents pain associated with gall-bladder contraction, probably by relaxation of the sphincter of Oddi. Caerulein has also been shown to reduce renal colic and the pain of intermittent claudication. Preliminary clinical studies with the weak, non-selective, CCK antagonist proglumide, indicate an enhancement of **morphine** analgesia. As yet, no studies have demonstrated analgesic effects of CCK antagonists in man when administered alone.(ABSTRACT TRUNCATED AT 400 WORDS)

L5 ANSWER 60 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1987:850 CAPLUS
DOCUMENT NUMBER: 106:850
TITLE: A new simple mouse model for the in vivo evaluation of cholecystokinin (CCK) antagonists: comparative potencies and durations of action of nonpeptide antagonists
AUTHOR(S): Lotti, Victor J.; Cerino, Deborah J.; Kling, Paul J.; Chang, Raymond S. L.
CORPORATE SOURCE: Dep. Microb. Pharmacometrics, Merck Sharp and Dohme Res. Lab., West Point, PA, 19486, USA
SOURCE: Life Sciences (1986), 39(18), 1631-8
CODEN: LIFSAK; ISSN: 0024-3205
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A new simple mouse assay for the in vivo evaluation of CCK antagonists which is based upon visual determination of the gastric emptying of a charcoal meal is described. CCK-8 [25126-32-3] (24 μg/kg, s.c.) but not

various other peptide and nonpeptide agents effectively inhibited gastric emptying in this test system. The effect of CCK-8 was antagonized by established peripheral CCK antagonists but not representative agents of various other pharmacol. classes. The rank order of potency of the CCK antagonists were: **L-364718** **[103420-77-5]** (ED50 = 0.01 mg/kg, i.v.; 0.04 mg/kg, p.o.) > compound 16 [97964-56-2] (ED50 = 1.5 mg/kg i.v.; 2.0 m/kg p.o.) > asperlicin [93413-04-8] (ED50 = 14.8 mg/kg i.v.) > proglumide [6620-60-6] (ED50 = 184 mg/kg i.v.; 890 mg/kg, p.o.). Duration of action studies based upon ED50 values determined at various time intervals after oral administration showed that L-364,718 and proglumide are considerably longer acting than compound 16. Asperlicin (ED50 >300 mg/kg, p.o.) was ineffective as a CCK antagonist when administered orally. These data provide the first direct comparisons of the in vivo potencies of current CCK antagonists and demonstrate the utility of a new simple mouse assay for the in vivo characterization of peripheral CCK antagonists.

L5 ANSWER 61 OF 166 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003499217 EMBASE
TITLE: **Opioid** hyperalgesia and tolerance versus 5-HT(1A) receptor-mediated inverse tolerance.
AUTHOR: Xu X.-J.; Colpaert F.; Wiesenfeld-Hallin Z.
CORPORATE SOURCE: Z. Wiesenfeld-Hallin, Department of Laboratory Medicine, Karolinska Institutet, Huddinge University Hospital, S-141 86 Stockholm, Sweden. zsuzsanna.wiesenfeld-hallin@neurophys.hs.sll.se
SOURCE: Trends in Pharmacological Sciences, (2003) 24/12 (634-639). Refs: 61
ISSN: 0165-6147 CODEN: TPHSDY
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB In addition to analgesia, **opioids** also produce paradoxical hyperalgesic effects following acute and chronic treatment. In this article, we review the occurrence of this hyperalgesia under several conditions, and discuss the potential mechanisms and clinical implications. We also review recent evidence that paradoxical analgesia and inverse tolerance induced by stimulation of 5-HT(1A) receptors, which is a mirror image of **opioid**-induced hyperalgesia and tolerance, might achieve clinically significant analgesia in chronic pain.

L5 ANSWER 62 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1998:717528 CAPLUS
DOCUMENT NUMBER: 130:61383
TITLE: Interactions between antinociception induced by cholecystokinin antagonists and GABA agonists in the tail-flick test
AUTHOR(S): Zarrindast, Mohammad-Reza; Rezayat, Mehdi; Ghanipoor, Nahid; Parvini, Shirin
CORPORATE SOURCE: Department of Pharmacology, School of Medicine, Tehran University of Medical Science, Tehran, 13145-784, Iran
SOURCE: Pharmacology & Toxicology (Copenhagen) (1998), 83(4), 143-148
CODEN: PHTOEH; ISSN: 0901-9928
PUBLISHER: Munksgaard International Publishers Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The aim of the study was to investigate the influences of cholecystokinin receptor antagonists L-365,260, **MK-329** and proglumide

on antinociception induced by baclofen and GABA uptake inhibitor 4,5,6,7-tetrahydroisoxazolo [4,5-c]pyridin-3-ol (THPO) in the tail flick test has been studied. Baclofen and THPO induced antinociception in the tail flick test. **Morphine**, and the CCK receptor antagonists, **MK-329**, L-365,260 and proglumide also induced antinociception. The CCK receptor antagonists potentiated antinociceptive response induced by both baclofen and THPO. It may be concluded that cholecystokinin receptor mechanism(s) may interact with antinociception induced by GABA receptor mechanism(s).

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 63 OF 166 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2001434496 EMBASE
TITLE: Evidence for ε- **opioid** receptor-mediated β-endorphin-induced analgesia.
AUTHOR: Tseng L.F.
CORPORATE SOURCE: L.F. Tseng, Dept. of Anesthesiology, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226, United States. Itseng@mcw.edu
SOURCE: Trends in Pharmacological Sciences, (1 Dec 2001) 22/12 (623-630).
Refs: 60
ISSN: 0165-6147 CODEN: TPHSDY
PUBLISHER IDENT.: S 0165-6147(00)01843-5
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Among the **opioid** receptors, which have been pharmacologically classified as μ, δ, κ and ε, the existence of the ε receptor has been controversial, and this receptor is generally not recognized as a member of the **opioid** peptide receptor family because it has not been precisely characterized. However, results from pharmacological, physiological and **opioid** receptor binding studies clearly indicate the presence of ε- **opioid** receptors, which are distinct from μ-, δ- or κ- **opioid** receptors. This putative ε- **opioid** receptor is stimulated supraspinally by the endogenous **opioid** peptide β-endorphin, which induces the release of Met-enkephalin, which, in turn, acts on spinal δ2- **opioid** receptors to produce antinociception. In this article, this β-endorphin-sensitive ε- **opioid** receptor-mediated descending pain control system, which is distinct from that activated by the μ- **opioid** receptor agonist **morphine**, is described and the physiological role of the β-endorphin-mediated system in pain control activated by cold-water swimming and intraplantar injection of formalin is discussed.

L5 ANSWER 64 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1990:30228 CAPLUS
DOCUMENT NUMBER: 112:30228
TITLE: Cholecystokinin-A receptor ligands based on the κ- **opioid** agonist tifluadom
AUTHOR(S): Bock, Mark G.; DiPardo, Robert M.; Evans, Ben E.; Rittle, Kenneth E.; Whitter, Willie L.; Veber, Daniel F.; Freidinger, Roger M.; Chang, Raymond S. L.; Chen, T. B.; Lotti, Victor J.
CORPORATE SOURCE: Dep. Med. Chem., Merck Sharp and Dohme Res. Lab., West Point, PA, 19486, USA
SOURCE: Journal of Medicinal Chemistry (1990), 33(1), 450-5
CODEN: JMCMAR; ISSN: 0022-2623

DOCUMENT TYPE: Journal
LANGUAGE: English
AB Tifluadom, a κ- **opioid** agonist and cholecystokinin-A (CCK-A) receptor antagonist, was utilized as a model to prepare a series of 2-(aminomethyl)- and 3-(aminomethyl)-1,4-benzodiazepines. These compds. were tested in vitro as inhibitors of the binding of [125I]CCK to rat pancreas and guinea pig brain receptors. All compds. with IC50's <100 μM proved to have greater affinity for the CCK-A receptor, with the most potent analog having an IC50 of 0.16 μM. The benzodiazepines described in this study are simultaneously CCK-A and **opioid** receptor ligands. The ramification of this dichotomy on current concepts of peptide hormone action are discussed. These results further demonstrate the versatility of the benzodiazepine core structure for designing nonpeptide ligands for peptide receptors and the ability to fine-tune the receptor interactions of these benzodiazepines by appropriate structure modifications.

L5 ANSWER 65 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:594617 CAPLUS
DOCUMENT NUMBER: 133:217964
TITLE: Role of cholecystokinin receptors in induction of antinociception in hot-plate test
AUTHOR(S): Rezayat, Mehdi; Rahnavard, Azita; Zarrindast, Mohammad-Reza
CORPORATE SOURCE: Department of Pharmacology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
SOURCE: Pharmacology & Toxicology (Copenhagen) (2000), 87(2), 58-62
CODEN: PHTOEH; ISSN: 0901-9928
PUBLISHER: Munksgaard International Publishers Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In the present study, the antinociceptive effect of cholecystokinin receptor agonists in the hot-plate test in mice has been evaluated. S.c. administration of cholecystokinin octapeptide (cholecystokinin-8; 0.001, 0.005, 0.01, 0.05, and 0.1 mg/kg), unsulfated cholecystokinin octapeptide (cholecystokinin-8U; 0.1 mg/kg) or caerulein (0.25 mg/kg) produced antinociception. Administration of the cholecystokinin tetrapeptide (cholecystokinin-4; 0.25, 0.5 and 1.0 mg/kg) had no effect in the hot-plate test. S.c. injection of the selective cholecystokinin receptor antagonists, **MK-329** (0.125, 0.25 and 0.5 mg/kg) or L-365,260 (0.125, 0.25 and 0.5 mg/kg), produced no antinociceptive response. When the animals were pretreated with the cholecystokinin receptor antagonists or naloxone (0.5 and 1 mg/kg), a significant decrease in the antinociceptive response induced by cholecystokinin-8 and caerulein was obtained. The results indicate that single administration of cholecystokinin receptor agonists could produce an antinociceptive effect which is probably mediated via cholecystokinin receptors. With respect to the results obtained from **morphine** and naloxone administration, it is concluded that there may be an interaction between cholecystokinin and **opiate** mechanisms.
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 66 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:855015 CAPLUS
DOCUMENT NUMBER: 123:247267
TITLE: Opposite role of CCKA and CCKB receptors in the modulation of endogenous enkephalin antidepressant-like effects
AUTHOR(S): Smadja, C.; Maldonado, R.; Turcaud, S.; Fournie-Zaluski, M. C.; Roques, B. P.
CORPORATE SOURCE: Dep. de Pharmacochimie Mol. et Structurale, UFR des Sciences Pharmaceutiques et Biologiques, Paris,

F-75270, Fr.
SOURCE: Psychopharmacology (Berlin) (1995), 120(4), 400-8
CODEN: PSCHDL; ISSN: 0033-3158
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Systemic administration of RB 101, a complete inhibitor of the enkephalin degrading enzymes, has been reported to induce naltrindole-reversed antidepressant-like effects in the conditioned suppression of mobility (CSM) test in mice. The selective CCKB antagonist L-365260 also elicits the same naltrindole-blocked responses on CSM. The aim of this study was therefore to investigate the possible modulation of RB 101 induced behavioral responses by activation or blockade of CCK receptors. Thus, the effects induced by RB 101 administered alone or associated with an ineffective dose of a selective CCKB agonist (BC 264), a CCKB agonist (L-365260) or a CCKA antagonist (**L-364718**), were evaluated on the CSM in mice. RB 101 alone decreased the stress-induced loss of motility, as previously reported. The antidepressant like effect of RB 101 was potentiated by L-365260, and suppressed by BC 264 and to a lesser extent by **L-364718**. The facilitatory effect induced by L-365260 on RB 101 responses was blocked by the delta selective antagonist naltrindole. All these effects occurred only in shocked animals. The present results suggest that the activation of CCKA and CCKB receptors by endogenous CCK, could play an opposite role in the control of behavioral responses induced by endogenous enkephalins. Delta **opioid** receptors seem to be selectively involved in this interaction.

L5 ANSWER 67 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1991:671132 CAPLUS
DOCUMENT NUMBER: 115:271132
TITLE: Differential involvement of CCK-A and CCK-B receptors in the regulation of locomotor activity in the mouse
AUTHOR(S): Vasar, E.; Harro, J.; Lang, A.; Pold, A.; Soosaar, A.
CORPORATE SOURCE: Inst. Gen. Mol. Pathol., Tartu Univ., Tartu, 202 400, USSR
SOURCE: Psychopharmacology (Berlin, Germany) (1991), 105(3), 393-9
CODEN: PSCHDL; ISSN: 0033-3158
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The influence of the CCK-A antagonist **devazepide** and the CCK-B/gastrin antagonist L-365,260 on the locomotor activity of mice was studied. **Devazepide** and L-365,260 had opposite effects on spontaneous locomotor activity, and on caerulein- and apo-**morphine** -induced hypomotility in the mouse. **Devazepide** in high doses (0.1-1 mg/kg i.p.) reduced spontaneous motor activity, whereas L-365,260 at a high dose (1 mg/kg i.p.) increased the activity of mice. **Devazepide** (0.1-10 μg/kg) moderately antagonized the sedative effect of apomorphine (0.1 mg/kg s.c.) and caerulein (25 μg/kg s.c.), whereas L-365,260 (1-10 μg/kg) significantly potentiated the actions of dopamine and CCK agonists. Concomitant administration fo caerulein (15 μg/kg s.c) and apomorphine (0.1 mg/kg s.c.) caused an almost complete loss of locomotor activity in the mouse. **Devazepide** and L-365,260 (0.1-10 μg/kg) were completely ineffective against caerulein-induced potentiation of apomorphine hypomotility. **Devazepide** in high doses (0.1-1 mg/kg), reducing the spontaneous motor activity of mice, counteracted the motor excitation induced by d-amphetamine (5 mg/kg i.p.). The CCK agonist caerulein (100 μg/kg s.c.) had a similar antiamphetamine effect. **Devazepide** (1-100 μg/kg) and L-365,260 (1 μg/kg) reversed completely the antiamphetamine effect of caerulein. The results of present study reflect apparently distinct role of CCK-A and CCK-B receptors in the regulation of motor activity. The opposite effect of **devazepide** and L-365,260

on caerulein- and apomorphine-induced hypolocomotion is probably related to the antagonistic role of CCK A and CCK-B receptor subtypes in the regulation of mesencephalic dopaminergic neurons. The antiamphetamine effect of caerulein is possibly linked to the stimulation of CCK-A receptors in the mouse brain, whereas the blockade of both subtypes of the CCK-8 receptor is involved in the antiamphetamine effect of **devazepide**.

L5 ANSWER 68 OF 166 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 94122823 EMBASE
DOCUMENT NUMBER: 1994122823
TITLE: Recent advances in **opioid** and non-**opioid** analgesia (1992-1993).
AUTHOR: Press J.B.; Raffa R.B.
CORPORATE SOURCE: RW Johnson Pharm. Research Institute, Welsh and McKean Roads,Spring House, PA 19477-0776, United States
SOURCE: Expert Opinion on Therapeutic Patents, (1994) 4/4 (379-393).
ISSN: 0962-2594 CODEN: EOTPEG
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
030 Pharmacology
031 Arthritis and Rheumatism
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English

L5 ANSWER 69 OF 166 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 92171466 EMBASE
DOCUMENT NUMBER: 1992171466
TITLE: Cholecystokinin antianalgesia: Safety cues abolish **morphine** analgesia.
AUTHOR: Wiertelak E.P.; Maier S.F.; Watkins L.R.
CORPORATE SOURCE: Department of Psychology, University of Colorado,Boulder, CO 80309, United States
SOURCE: Science, (1992) 256/5058 (830-833).
ISSN: 0036-8075 CODEN: SCIEAS
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
003 Endocrinology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Environmental stimuli that signal the occurrence of aversive or dangerous events activate endogenous **opiate** analgesia systems. Signals for safety (the nonoccurrence of aversive events) produce the opposite and inhibit environmentally produced analgesia. Stimuli that signal safety are now shown to abolish the analgesic effect of **morphine**, even when **morphine** is applied directly to spinal cord. Further, this antiopiate effect occurs because the environmental stimulus leads to release of the neuropeptide cholecystokinin in the spinal cord. This process may contribute to the regulation of pain and the development of **opiate** tolerance.

L5 ANSWER 70 OF 166 USPATFULL on STN
ACCESSION NUMBER: 2003:127094 USPATFULL
TITLE: Methods for identifying novel multimeric agents that modulate receptors
INVENTOR(S): Christensen, Burton G., Alamo, CA, UNITED STATES

Griffin, John H., Atherton, CA, UNITED STATES
Jenkins, Thomas E., La Honda, CA, UNITED STATES
Judice, J. Kevin, El Granada, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003087306	A1	20030508
APPLICATION INFO.:	US 2001-15534	A1	20011213 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2000-493462, filed on 28 Jan 2000, ABANDONED Continuation of Ser. No. US 1999-327904, filed on 8 Jun 1999, ABANDONED

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-92938P	19980715 (60)
	US 1998-88466P	19980608 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: THERAVANCE, INC., 901 GATEWAY BOULEVARD, SOUTH SAN FRANCISCO, CA, 94080
NUMBER OF CLAIMS: 35
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 52 Drawing Page(s)
LINE COUNT: 8387
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed are novel multi-binding compounds (agents) which bind cellular receptors. The compounds of this invention comprise a plurality of ligands each of which can bind to such cellular receptors thereby modulating the biological processes/functions thereof. Each of the ligands is covalently attached to a linker or linkers which may be the same of different to provide for the multi-binding compound. The linker is selected such that the multi-binding compound so constructed demonstrates increased modulation or disruption of the biological processes/functions of the cell. Also disclosed is a method for identifying such novel multi-binding compounds which bind cellular receptors and a method for generating a mixture of such novel multi-binding compounds.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 71 OF 166 MEDLINE on STN
ACCESSION NUMBER: 1998125940 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9466464
TITLE: Cholecystokinin inhibits peripheral **opioid** analgesia in inflamed tissue.
AUTHOR: Schafer M; Zhou L; Stein C
CORPORATE SOURCE: Behavioral Pharmacology and Genetics Section, Division of Intramural Research, National Institute on Drug Abuse, Baltimore, MD 21224, USA.
CONTRACT NUMBER: RO1NS32466 (NINDS)
SOURCE: Neuroscience, (1998 Jan) 82 (2) 603-11.
Journal code: 7605074. ISSN: 0306-4522.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 19980319
Last Updated on STN: 20000303
Entered Medline: 19980311

AB There is abundant evidence that **opioid** receptors are present on peripheral terminals of primary afferent neurons. Experimental and clinical studies have shown that activation of these peripheral **opioid** receptors produces potent analgesia. In addition to

peripheral **opioid** receptors, cholecystokinin receptors are present in sensory neurons. We examined the hypothesis that cholecystokinin receptors may be present on the same primary afferent neuron and that either exogenous or endogenous cholecystokinin may modulate peripheral antinociceptive effects of mu-**opioid** receptor agonists. Administration of cholecystokinin into inflamed paws, of the rat, but not intravenously attenuated peripheral antinociceptive effects induced by two mu-**opioid** receptor agonists, [D-Ala2,N-methyl-Phe4,Gly-ol5]-enkephalin and fentanyl. Only the desulphated form of cholecystokinin produced significant and dose-dependent attenuation. Cholecystokinin alone did not alter nociceptive baseline values in inflamed or non-inflamed paws. The anti-**opioid** effect of cholecystokinin was dose-dependently antagonized by the cholecystokininB receptor-selective antagonist L-365260, but not by the cholecystokininA receptor-selective antagonist **L-364718**. Local pretreatment with the protein kinase C specific inhibitor calphostin C abolished cholecystokinin's effect. Peripheral antinociceptive effects of [D-Ala2,N-methyl-Phe4,Gly-ol5]-enkephalin and fentanyl were not altered by intraplantar L-365260 alone. These results indicate that activation of peripheral cholecystokininB but not cholecystokininA receptors attenuates the local antinociceptive effects of mu-**opioid** receptor agonists in inflamed tissue. This anti-**opioid** effect may be mediated by protein kinase C in sensory nerve terminals. Endogenous cholecystokinin does not seem to influence the efficacy of peripheral **opioids** under both normal and inflammatory conditions.

L5 ANSWER 72 OF 166 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2004026597 EMBASE
TITLE: Cholecystokinin antagonists a new way to improve the analgesia from old analgesics?.
AUTHOR: McCleane G.
CORPORATE SOURCE: G. McCleane, Rampark Pain Centre, 2 Rampark, Dromore Road, Lurgan BT66 7JH, United Kingdom. gary@mccleane.freeserve.co.uk
SOURCE: Current Pharmaceutical Design, (2004) 10/3 (303-314). Refs: 106
ISSN: 1381-6128 CODEN: CPDEFP
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Cholecystokinin, originally thought to be confined only to the gastrointestinal tract, is now known to be co-localised in both the gastrointestinal tract and central nervous system. In animal models levels are increased after neural injury and with **opioid** administration. This peptide acts as an anti-**opioid**, and as levels increase, the extent of **opioid** derived antinociception decreases. Co-administration of a CCK antagonist along with an **opioid** is associated with an improved level of antinociception. Furthermore CCK antagonists may prevent antinociceptive tolerance with **opioids** and even reverse established tolerance Human studies have now confirmed the pro-analgesic effect of some CCK antagonists. Human investigation of the effect of CCK antagonists on analgesic tolerance has yet to be performed. This review examines the available evidence that suggests a role for CCK antagonists in human pain management.

L5 ANSWER 73 OF 166 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 1999188465 EMBASE
TITLE: BOC-CCK-4, CCK(B) receptor agonist, antagonizes anxiolytic-like action of **morphine** in elevated plus-maze.
AUTHOR: Koks S.; Soosaar A.; Voikar V.; Bourin M.; Vasar E.
CORPORATE SOURCE: Dr. S. Koks, Department of Physiology, University of Tartu, 2 Naituse Street, EE2400 Tartu, Estonia. sulev.koks@ut.ee
SOURCE: Neuropeptides, (1999) 33/1 (63-69).
Refs: 25
ISSN: 0143-4179 CODEN: NRPPDD
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB This study investigated a role of cholecystokinin (CCK) in the anxiolytic-like action of **morphine**, an agonist of μ-**opioid** receptors, in the rat plus-maze model of anxiety. The acute administration of **morphine** (1 mg/kg) induced a significant increase of exploratory activity in the plus- maze, but did not affect the locomotor activity in the motility test. The higher dose of **morphine** (2.5 mg/kg) tended to decrease the locomotor activity and, therefore, did not cause the anxiolytic-like action in the plus-maze. The other drugs (naloxone, BOC-CCK-4, L-365,260) and their combinations with **morphine** (0.5-1 mg/kg) did not affect the locomotor activity of rats. The **opioid** antagonist naloxone itself (0.5 mg/kg) did not change the exploratory activity in the plus-maze, but potently antagonized the anxiolytic-like action of **morphine** (1 mg/kg). An agonist of CCK(B) receptors BOC-CCK-4 (1-50 μg/kg) induced a dose-dependent anxiogenic-like action in the plus-maze. Nevertheless, only one dose of BOC-CCK-4 (10 μg/kg) completely reversed the action of **morphine**. Also, one dose of CCK(B) receptor antagonist L-365,260 (10 μg/kg) was effective to modify the behaviour of rats in the elevated plus-maze. Namely, this dose of L-365,260 increased the ratio between open and total arm entries, a behavioural measure believed to reflect the anxiolytic-like action in the elevated plus-maze. The combination of L- 365,260 (100 μg/kg) with the sub-effective dose of **morphine** (0.5 mg/kg) caused the anxiolytic-like action in the plus-maze not seen if the drugs were given alone. In conclusion, **morphine** induces a potent anxiolytic-like action in the elevated plus-maze and CCK is acting as an endogenous antagonist of this effect of **morphine**.

L5 ANSWER 74 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:537420 CAPLUS
DOCUMENT NUMBER: 133:261762
TITLE: A cholecystokinin receptor antagonist blocks milk-induced but not maternal-contact-induced decrease of ultrasonic vocalization in rat pups
AUTHOR(S): Weller, Aron; Gispan, Iris H.
CORPORATE SOURCE: Developmental Psychobiology Laboratory Department of Psychology, Bar Ilan University, Ramat Gan, Israel
SOURCE: Developmental Psychobiology (2000), 37(1), 35-43
CODEN: DEPBA5; ISSN: 0012-1630
PUBLISHER: John Wiley & Sons, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The role of cholecystokinin (CCK) in reducing separation-induced ultrasonic vocalization (USV) was examined by peripheral administration of the selective CCKA receptor antagonist **devazepide** to 10-11-day-old rats. Pups placed alone for 2 min emitted a mean of 55.1 USV/min. When placed on a paper towel wet with warm, sweet milk, USV rate decreased to

23.2/min for the following 8 min. **Devazepide** (150-600 μg/kg, i.p.) prevented this USV reduction, but did not increase feeding. In contrast, USV reduction produced by contact with the anesthetized dam was not affected by **devazepide**. Similarly, the **opiate** antagonist naltrexone (0.5 and 1.0 mg/kg) has been shown to block **morphine**-induced USV decrease in pups away from the dam, but was ineffective when USV reduction was induced by the presence of the dam (E. M. Blass et al., 1990; S. Carden & M. Hofer, 1990). The current findings suggest that CCK's role is specific, in that it mediates milk- but not dam-induced quieting of USV. The results, however, are not incompatible with the possibility that CCK and **opioids** are part of multiple, redundant pathways that mediate the quieting of USV by the dam.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 75 OF 166 EMBASE on STN

ACCESSION NUMBER: 2003283766 EMBASE

TITLE: Modulation of visceral hyperalgesia by **morphine** and cholecystokinin from the rat rostroventral medial medulla.

AUTHOR: Friedrich A.E.; Gebhart G.F.

CORPORATE SOURCE: G.F. Gebhart, Department of Pharmacology, College of Medicine, University of Iowa, Iowa City, IA 52242, United States. gf-gebhart@uiowa.edu

SOURCE: Pain, (2003) 104/1-2 (93-101).
Refs: 71
ISSN: 0304-3959 CODEN: PAINDB

COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 008 Neurology and Neurosurgery
037 Drug Literature Index
048 Gastroenterology

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Using a model of visceral nociception, we examined whether cholecystokinin (CCK) acts as an anti-**opioid** peptide in the rat rostral ventromedial medulla (RVM). Because such interaction may be affected by inflammation, rats with and without inflamed colons were studied. The visceromotor response to noxious colorectal distension (CRD), quantified electromyographically, was recorded before and after intra-RVM administration of CCK, CCK receptor antagonists, and **morphine**. Either 50% ethanol/saline (vehicle) or 2,4,6-trinitrobenzenesulfonic acid (TNBS), which inflames the colon, was instilled into the colon 5 days before experiments. Intra-RVM **morphine** dose-dependently attenuated responses to CRD in intracolonic vehicle-treated rats. In TNBS-treated rats with inflamed colons, responses to CRD were significantly increased and 0.3, 3.0 and 6.0μg doses of intra-RVM **morphine** reduced responses to control (i.e. were anti-hyperalgesic); the greatest dose tested (30μg) further reduced responses to 40% control. In intracolonic vehicle-treated rats, intra-RVM pre-treatment with a selective CCK(B) (but not CCK(A)) receptor antagonist dose-dependently and significantly enhanced the effect of a low dose of **morphine**. Intra-RVM CCK-8 peptide enhanced responses to CRD in intracolonic vehicle-treated, but not TNBS-treated rats. Intra-RVM naloxone was without effect in intracolonic vehicle-or TNBS-treated rats, suggesting an absence of tonic **opioid** activity in RVM. These results document a CCK-**opioid** interaction in RVM, suggesting that colon inflammation leads to tonic activity at CCK(B) receptors in RVM. .COPYRGT. 2003 International Association for the Study of Pain. Published by Elsevier Science B.V. All rights reserved.

L5 ANSWER 76 OF 166 EMBASE on STN

ACCESSION NUMBER: 1999286857 EMBASE
TITLE: Signal transduction in neuropathic pain, with special emphasis on the analgesic role of **opioids** - Part II: Moving basic science towards a new pharmacotherapy.
AUTHOR: McCormack K.
CORPORATE SOURCE: K. McCormack, Drug Research Group, McCormack Limited, Church House, Church Square, Leighton Buzzard, Beds. LU7 7AE, United Kingdom
SOURCE: Pain Reviews, (1999) 6/2 (99-131).
Refs: 326
ISSN: 0968-1302 CODEN: PAREFV
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 008 Neurology and Neurosurgery
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB In the first part of this three-part article I explored the notion that pharmacological intervention, aimed at eliminating abnormal sensations such as hyperalgesia or paraesthesia arising as a direct result of nerve injury, activates adaptive responses that ensure adequacy of neurotransmission, regardless of whether such transmission ultimately evokes normal or abnormal sensations. Thus, by their nature, such adaptive responses will act to oppose and surmount any drug-induced intervention designed to diminish pain through attenuation of signal conduction. A corollary of this hypothesis is that even the most sophisticated novel pharmacological entities, when used to block the pain signal, represent substrates for evoking a repertoire of failsafe mechanisms that have evolved throughout a history of challenge and response. In Part II, I explore in greater depth how activation of these responses may explain why the treatment of neuropathic pains, particularly with **opioids**, can be so frustrating.

L5 ANSWER 77 OF 166 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 96362037 EMBASE
DOCUMENT NUMBER: 1996362037
TITLE: Association of enkephalin catabolism inhibitors and CCK-B antagonists: A potential use in the management of pain and **opioid** addiction.
AUTHOR: Roques B.P.; Noble F.
CORPORATE SOURCE: Dept. de Pharmacochimie Moleculaire, INSERM U266-CNRS URA D 1500, Universite Rene Descartes, 4, Avenue de l'Observatoire,75270 Paris Cedex 06, France
SOURCE: Neurochemical Research, (1996) 21/11 (1397-1410).
ISSN: 0364-3190 CODEN: NEREDZ
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The overlapping distribution of **opioid** and cholecystokinin (CCK) peptides and their receptors (μ and δ **opioid** receptors; CCK-A and CCK-B receptors) in the central nervous system have led to a large number of studies aimed at clarifying the functional relationships between these two neuropeptides. Most of the pharmacological studies devoted to the role of CCK and enkephalins have been focused on the control of pain. Recently the existence of regulatory mechanisms between both systems have been proposed, and the physiological antagonism between CCK and endogenous **opioid** systems has been definitely

demonstrated by coadministration of CCK-B selective antagonists with RB 101, a systemically active inhibitor, which fully protects enkephalins from their degradation. Several studies have also been done to investigate the functional relationships between both systems in development of **opioid** side-effects and in behavioral responses. This article will review the experimental pharmacology of association of enkephalin-degrading enzyme inhibitors and CCK-B antagonists to demonstrate the interest of these molecules in the management of both pain and **opioid** addiction.

L5 ANSWER 78 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:392318 CAPLUS
DOCUMENT NUMBER: 140:400077
TITLE: Pharmaceutical combinations including either a 5-HT4 receptor agonist or antagonist or a 5-HT3 receptor antagonist and a co-agent and their use in treating gastrointestinal and abdominal visceral disorders
INVENTOR(S): Billstein, Stephan Anthony; Dumovic, Peter; Franco, Nicola; Iwicki, Mark Thomas; Pfannkuche, Hans-Jurgen; Wilusz, Edward Joseph
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 14 pp., Cont.-in-part of U.S. Ser. No. 722,784, abandoned.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2004092511	A1	20040513	US 2003-702688		20031106
PRIORITY APPLN. INFO.:			US 1999-266333P	P	19991210
			US 2000-722784	B1	20001127

AB The invention discloses a combination of a first agent including either a 5-HT4 receptor agonist or antagonist or a 5-HT3 receptor antagonist and a co-agent and pharmaceutical compns. and formulations containing the combination. The invention also discloses a method for treating a gastrointestinal and abdominal visceral disorder by administering the pharmaceutical compns. to a patient. The pharmaceutical compns. may also be employed as laxatives, to prepare a patient for colonoscopy and to regulate and stabilize enterochromaffin cell secretory, pain and motility mechanisms, afferent fiber activity and GI and lower abdominal smooth muscle cells. The dosage is preferably oral and administration is preferably once or twice a day. The preferred first agent is tegaserod.

L5 ANSWER 79 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:45450 CAPLUS
DOCUMENT NUMBER: 130:277056
TITLE: Effects of CCK antagonists on GABA mechanism-induced antinociception in the formalin test
AUTHOR(S): Rezayat, Mehdi; Tabarrai, Esmail; Parvini, Shirin; Zarrindast, Mohammad-Reza; Pirali, Morteza
CORPORATE SOURCE: School of Medicine, Department of Pharmacology, Tehran University of Medical Science, Tehran, Iran
SOURCE: European Neuropsychopharmacology (1999), 9(1-2), 9-14
CODEN: EURNE8; ISSN: 0924-977X
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In this work, the influences of CCK receptor antagonists on antinociception induced by the GABA receptor agonist, baclofen, and the GABA uptake inhibitor, THPO, in the formalin test have been studied. GABA-B agonist baclofen (0.75, 1.25 and 2.5 mg/kg), THPO, a GABA uptake

inhibitor (1 and 2 mg/kg) and **morphine** (1.5, 3 and 6 mg/kg) induced antinociception in both phases of the formalin test in mice. The selective CCK receptor antagonists, L-365260, **MK-329** (0.05, 0.125 and 0.25 mg/kg) and non-selective CCK receptor antagonist, proglumide (2.5, 5, 10 and 20 mg/kg) induced antinociception only in high doses. The CCK receptor antagonists potentiated baclofen (0.75, 1.25 and 2.5 mg/kg) or THPO (1 and 2 mg/kg) responses. It may be concluded that the CCK receptor mechanism may interact with GABA-function in its antinociceptive effect.

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 80 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1991:74697 CAPLUS
DOCUMENT NUMBER: 114:74697
TITLE: Cholecystokinin-A receptor ligands based on the κ- **opioid** agonist tifluadom [Erratum to document cited in CA112(5):30228d]
AUTHOR(S): Bock, Mark G.; DiPardo, Robert M.; Evans, Ben E.; Rittle, Kenneth E.; Whitter, Willie L.; Veber, Daniel F.; Freidinger, Roger M.; Chang, Raymond S. L.; Chen, T. B.; Lotti, Victor J.
CORPORATE SOURCE: Dep. Med. Chem., Merck Sharp and Dohme Res. Lab., West Point, PA, 19486, USA
SOURCE: Journal of Medicinal Chemistry (1990), 33(9), 2679
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
AB An error in structure 2 has been corrected The error was reflected in the index entries.

L5 ANSWER 81 OF 166 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 94153991 EMBASE
DOCUMENT NUMBER: 1994153991
TITLE: SNF9007: A novel analgesic that acts simultaneously at delta1, delta2 and mu **opioid** receptors.
AUTHOR: Williams C.L.; Rosenfeld G.C.; Dafny N.; Fang S.-N.; Hruby V.J.; Bowden G.; Cullinan C.A.; Burks T.F.
CORPORATE SOURCE: Department of Pharmacology, Univ. of Texas Health Science Center, P.O. Box 20708,Houston, TX 77225, United States
SOURCE: Journal of Pharmacology and Experimental Therapeutics, (1994) 269/2 (750-755).
ISSN: 0022-3565 CODEN: JPETAB
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Intracerebroventricular administration of the synthetic cholecystokinin analog SNF9007 (Asp-Tyr-D-Phe-Gly-Trp-[NMe]-Nle-Asp-Phe-NH2) produced antinociception in the mouse hot-plate and warm water tail-flick tests. The mechanisms of its analgesic actions were assessed by administering antagonists selective for CCK (cholecystokinin octapeptide, sulfated)-A and CCK-B receptors, as well as specific antagonists for the mu **opioid** receptor (D-Phe-Cys-Tyr-D-Trp-Arg-Thr-Pen-Thr-NH2, 1 μg i.c.v.), the delta-1 **opioid** receptor [D-Ala2-Leu5, Cys6)enkephalin, 4.57 nmol i.c.v., 24 hr pretreatment), the delta-2 **opioid** receptor (naltrindole benzofuran, 25 pmol i.c.v.) and the kappa **opioid** receptor (nor-binaltorphimine, 10 mg/kg s.c.). The antinociceptive activity of SNF9007 was not a result of the activation of CCK receptors, as treatment with either CCK-A or CCK-B receptor antagonist was ineffective in blocking SNF9007 antinociception. Nor-binaltorphimine

and naltrindole benzofuran were completely ineffective in blocking SNF9007 antinociception when administered alone or in combination. However, co-administration of delta-1 or delta-2 **opioid** receptor antagonists with the mu **opioid** receptor antagonist D-Phe-Cys-Tyr-D-Trp-Arg-Thr-Pen-Thr-NH2 resulted in a dramatic reduction in analgesic response to SNF9007. Furthermore, the co-administration of mu + delta-1 + delta-2 **opioid** receptor antagonists resulted in an even greater inhibition of SNF9007 antinociception (>10-fold shift). We conclude that SNF9007 acts simultaneously at brain delta-1, delta- 2 and mu **opioid** receptors to induce antinociceptive effects in mice.

L5 ANSWER 82 OF 166 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2002099781 EMBASE
TITLE: The biology of the **opioid** growth factor receptor (OGFr).
AUTHOR: Zagon I.S.; Verderame M.F.; McLaughlin P.J.
CORPORATE SOURCE: I.S. Zagon, Milton S. Hershey Medical Center, Pennsylvania State University, College of Medicine, 500 University Drive, Hershey, PA 17033, United States. isz1@psu.edu
SOURCE: Brain Research Reviews, (2002) 38/3 (351-376).
Refs: 159
ISSN: 0165-0173 CODEN: BRERD2
PUBLISHER IDENT.: S 0165-0173(01)00160-6
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB **Opioid** peptides act as growth factors in neural and non-neural cells and tissues, in addition to serving for neurotransmission/neuromodulation in the nervous system. The native **opioid** growth factor (OGF), [Met(5)]-enkephalin, is a tonic inhibitory peptide that plays a role in cell proliferation and tissue organization during development, cancer, cellular renewal, wound healing, and angiogenesis. OGF action is mediated by a receptor mechanism. Assays with radiolabeled OGF have detected specific and saturable binding, with a one-site model of kinetics. Subcellular fractionation studies show that the receptor for OGF (OGFr) is an integral membrane protein associated with the nucleus. Using antibodies generated to a binding fragment of OGFr, this receptor has been cloned and sequenced in human, rat, and mouse. OGFr is distinguished by containing a series of imperfect repeats. The molecular and protein structure of OGFr have no resemblance to that of classical **opioid** receptors, and have no significant homologies to known domains or functional motifs with the exception of a bipartite nuclear localization signal. Immunoelectron microscopy and immunocytochemistry investigations, including co-localization studies, have detected OGFr on the outer nuclear envelope where it interfaces with OGF. The peptide-receptor complex associates with karyopherin, translocates through the nuclear pore, and can be observed in the inner nuclear matrix and at the periphery of heterochromatin of the nucleus. Signal transduction for modulation of DNA activity is dependent on the presence of an appropriate confirmation of peptide and receptor. This report reviews the history of OGF-OGFr, examines emerging insights into the mechanisms of action of **opioid** peptide-receptor interfacing, and discusses the clinical significance of these observations. .COPYRGT. 2002 Elsevier Science B.V. All rights reserved.

L5 ANSWER 83 OF 166 MEDLINE on STN

ACCESSION NUMBER: 2000075286 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10607394
TITLE: A locus and mechanism of action for associative

morphine tolerance.
AUTHOR: Mitchell J M; Basbaum A I; Fields H L
CORPORATE SOURCE: Department of Physiology, University of California, San Francisco, San Francisco, California 94143-0444, USA.
CONTRACT NUMBER: DA 01949 (NIDA)
NS 21445 (NINDS)
SOURCE: Nature neuroscience, (2000 Jan) 3 (1) 47-53.
Journal code: 9809671. ISSN: 1097-6256.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000204
Last Updated on STN: 20000204
Entered Medline: 20000124

AB Repeated administration of an **opioid** in the presence of specific environmental cues can induce tolerance specific to that setting (associative tolerance). Prolonged or repeated administration of an **opioid** without consistent contextual pairing yields non-associative tolerance. Here we demonstrate that cholecystokinin acting at the cholecystokinin-B receptor is required for associative but not non-associative **morphine** tolerance. **Morphine** given in the **morphine**-associated context increased Fos-like immunoreactivity in the lateral amygdala and hippocampal area CA1. Microinjection of the cholecystokinin B antagonist L-365,260 into the amygdala blocked associative tolerance. These results indicate that cholecystokinin acting in the amygdala is necessary for associative tolerance to **morphine**'s analgesic effect.

L5 ANSWER 84 OF 166 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 94311087 EMBASE
DOCUMENT NUMBER: 1994311087
TITLE: Diversity of agents that modify **opioid** tolerance, physical dependence, abstinence syndrome, and self-administrative behavior.
AUTHOR: Bhargava H.N.
CORPORATE SOURCE: Pharmaceutics/Pharmacodynamics Dept., College of Pharmacy, University of Illinois, 833 South Wood Street,Chicago, IL 60612, United States
SOURCE: Pharmacological Reviews, (1994) 46/3 (293-324).
ISSN: 0031-6997 CODEN: PAREAQ
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
040 Drug Dependence, Alcohol Abuse and Alcoholism
LANGUAGE: English

L5 ANSWER 85 OF 166 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 92181662 EMBASE
DOCUMENT NUMBER: 1992181662
TITLE: Cholecystokinin administered intrathecally selectively antagonizes intracerebroventricular β-endorphin-induced tail-flick inhibition in the mouse.
AUTHOR: Tseng L.F.; Collins K.A.
CORPORATE SOURCE: Dept. of Pharmacology and Toxicology, Medical College of Wisconsin, P.O. Box 26509,Milwaukee, WI 53226, United States
SOURCE: Journal of Pharmacology and Experimental Therapeutics, (1992) 260/3 (1086-1092).
ISSN: 0022-3565 CODEN: JPETAB

COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The effects of sulfated cholecystokinin octapeptide (CCK8s) given intrathecally (i.t.) or intracerebroventricularly (i.c.v.) on inhibition of the tail-flick and paw-licking hot-plate responses induced by β-endorphin, **morphine**, D-Ala2-N-Me-Phe4-Gly-ol-Enkephalin (DAMGO) and D-Pen2-D-Pen5- Enkephalin (DPDPE), given i.t. or i.c.v., were studied in male ICR mice. CCK8s (1 ng) given i.t. effectively antagonized inhibition of the tail-flick response induced by i.c.v. administered β-endorphin (2 μg) and DPDPE (10 μg) but not **morphine** (4 μg) or DAMGO (0.02 μg). However, CCK8s given i.t. did not affect inhibition of the hot-plate response induced by any of the **opioid** agonists. CCK8s (0.2-40 ng) in combination with β-endorphin (2 μg) or **morphine** (4 μg) given i.c.v. did not affect β-endorphin- or **morphine**- induced inhibition of the tail-flick and hot-plate responses. CCK8s and its fragments given i.t. attenuated i.c.v. β-endorphin-induced tail-flick inhibition with different potencies and efficacies. CCK8s was the most potent compound in antagonizing i.c.v. β-endorphin-induced tail-flick inhibition. The rank order of potencies was CCK8s > CCK(27-33) >> caerulein. All three compounds were efficacious, whereas CCK(30-33) was not, in antagonizing β- endorphin-induced tail-flick inhibition. Intrathecal administration of CCK8s (1 ng) significantly attenuated the tail-flick inhibition induced by i.t. β- endorphin (0.5-1 μg) and DPDPE (5 μg) but not **morphine** (0.5-1 μg), DAMGO (5 ng), norepinephrine (5 ng) or serotonin (16 μg). The inhibition of the hot-plate response induced by i.t. administration of these agonists was not affected by i.t. CCK8s. The inhibitory effect of CCK8s given i.t. on i.c.v. β-endorphin-induced tail-flick inhibition is mediated by stimulation of cholecystokinin receptors, because the respective cholecystokinin A and B receptor blockers L364,718 (0.25-15 pg) and L365,260 (3-100 pg), given i.t., dose-dependently antagonized the effect caused by CCK8s. It is concluded that CCK8s given i.t. selectively attenuates i.c.v. β-endorphin-induced inhibition of the tail-flick response by inhibiting descending ε- **opioid** system activated by supraspinally applied β-endorphin.

L5 ANSWER 86 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:340357 CAPLUS
DOCUMENT NUMBER: 122:96923
TITLE: CCKA, but not CCKB, agonists suppress the hyperlocomotion induced by endogenous enkephalins, protected from enzymic degradation by systemic RB 101
AUTHOR(S): Dauge, Valerie; Corringer, Pierre-Jean; Roques, Bernard P.
CORPORATE SOURCE: UFR des Sciences Pharmaceutiques et Biologiques, Univ. Rene Descartes, Paris, Fr.
SOURCE: Pharmacology, Biochemistry and Behavior (1995), 50(2), 133-9
CODEN: PBBHAU; ISSN: 0091-3057
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Interactions between CCKergic and enkephalinergic systems were studied in mice using behavioral responses measured in Animex. The hyperlocomotion induced by 5 mg/kg of RB 101, a mixed inhibitor of enkephalin-degrading enzymes able to cross the blood-brain barrier, was previously shown to be mediated by δ- **opioid** receptor stimulation. The i.p. administration of a CCKA agonist, Boc-Tyr-Lys-(CONH-o-tolyl)-Asp-Phe-NH2

(0.1, 1, 10 μg/kg), suppressed the hyperlocomotion produced by i.v. injection of 5 mg/kg of RB 101. The effect of the CCKA agonist was suppressed by a selective CCKA antagonist, **devazepide**, injected i.p. at doses of 20 and 200 μg/kg and was potentiated by the selective δ- **opioid** agonist naltrindole at doses of 0.03 mg/kg. The i.p. injection of the selective CCKB agonist BC 264 (0.1-1 mg/kg) did not modify the RB 101-induced hyperlocomotor effect. These results reinforce the observed physiol. antagonism between the endogenous CCK and **opioid** systems but are at variance with the responses measured in stressful conditions. It is concluded that CCKA, but not CCKB, receptor activation counteracts the **opioid**-related hyperlocomotion.

L5 ANSWER 87 OF 166 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER: 1989:485671 BIOSIS
DOCUMENT NUMBER: PREV198937106790; BR37:106790
TITLE: INFLUENCE OF **L-364718** A SPECIFIC CCK-A ANTAGONIST ON PAIN THRESHOLD **MORPHINE** ANALGESIA AND **OPIOID** RECEPTORS.
AUTHOR(S): MARRAMA D [Reprint author]; POGGIOLI R; VERGONI A V; SANDRINI M; BERTOLINI A
CORPORATE SOURCE: INST PHARMACOL, UNIV MODENA, VIA G CAMPI 287, 41100 MODENA, ITALY
SOURCE: Pharmacological Research, (1989) Vol. 21, No. 4, pp. 473-474.
Meeting Info.: 2ND INTER-REGIONAL MEETING OF THE ITALIAN PHARMACOLOGICAL SOCIETY, EMILIA-ROMAGNA, MARCHE, FRIULI-VENEZIA GIULIA, TRENTINO-ALTO ADIGE, VENETO, MODENA, ITALY, DECEMBER 15, 1988. PHARMACOL RES.
CODEN: PHMREP. ISSN: 1043-6618.
DOCUMENT TYPE: Conference; (Meeting)
FILE SEGMENT: BR
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 26 Oct 1989
Last Updated on STN: 5 Dec 1989

L5 ANSWER 88 OF 166 USPATFULL on STN

ACCESSION NUMBER: 94:55545 USPATFULL
TITLE: Benzodiazepine analogs
INVENTOR(S): Bock, Mark G., Hatfield, PA, United States
Evans, Ben E., Lansdale, PA, United States
Freidinger, Roger M., Lansdale, PA, United States
PATENT ASSIGNEE(S): Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5324726		19940628
APPLICATION INFO.:	US 1992-968624		19921029 (7)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1992-824764, filed on 17 Jan 1992, now abandoned which is a continuation of Ser. No. US 1990-621500, filed on 7 Dec 1990, now abandoned which is a continuation-in-part of Ser. No. US 1989-452012, filed on 18 Dec 1989, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Berch, Mark L.
LEGAL REPRESENTATIVE: Daniel, Mark R., DiPrima, Joseph F.
NUMBER OF CLAIMS: 4
EXEMPLARY CLAIM: 1
LINE COUNT: 1217
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Benzodiazepine analogs of the formula: ##STR1## wherein: R.sup.3 is ##STR2## --NH(CH.sub.2).sub.2 --.sub.3 NHCOR.sup.7, ##STR3## or

--X.sup.11 NR.sup.18 SO.sub.2 (CH.sub.2).sub.q R.sup.7 ; R.sup.7 is O,S,HH, or NR.sup.15 with the proviso that X.sup.7 can be NR.sup.15 only when R.sup.1 is not H.

are disclosed which are antagonists of gastrin and cholecystokinin (CCK) with enhanced aqueous solubility and have properties useful in the treatment of disorders of gastric secretion, appetite regulation, gastrointestinal motility, pancreatic secretion, and dopaminergic function, as well as in treatment producing potentiation of **morphine** and other **opiate** analgesics.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 89 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:270788 CAPLUS
DOCUMENT NUMBER: 126:325409
TITLE: Antinociceptive effects of RB101, a complete inhibitor of enkephalin-catabolizing enzymes, are enhanced by a cholecystokinin type B receptor antagonist, as revealed by noxiously evoked spinal c-Fos expression in rats
AUTHOR(S): Honore, Prisca; Buritova, Jaroslava; Fournie-Zaluski, Marie-Claude; Roques, Bernard P.; Besson, Jean-Marie
CORPORATE SOURCE: Physiopharmacologie Systeme Nerveux, Inst. national Sante Recherche Medicale, Paris, 75014, Fr.
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1997), 281(1), 208-217
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of RB101, a complete inhibitor of enkephalin-catabolizing enzymes, alone or with a selective cholecystokinin (CCK)B receptor antagonist (CI988) or CCKA receptor antagonist (**devazepide**), on carrageenin-induced spinal c-Fos expression were investigated. Spinal c-Fos expression was observed 90 min after intraplantar carrageenin (6 mg/150 μl saline), with Fos-like-immunoreactive neurons preferentially located in the superficial laminae of the spinal dorsal horn. I.v. RB101 (10, 20 and 40 mg/kg) dose-dependently reduced the number of superficial Fos-like-immunoreactive neurons (r2=0.739), with 63% reduction for the highest dose. These effects were completely blocked by coadministered naloxone. Coadministration of inactive doses of i.v. RB101 (5 mg/kg) and i.p. CI988 (3 mg/kg) significantly and strongly reduced the number of carrageenin-induced, superficial, Fos-like-immunoreactive neurons (55% reduction of control carrageenin c-Fos expression). This effect was blocked by coadministered naloxone. It is important to note that coadministered RB101 and **devazepide** did not influence spinal c-Fos expression. None of the various drug combinations influenced the carrageenin-induced peripheral edema. These results show that RB101 dose-dependently decreases carrageenin-evoked spinal c-Fos expression. In addition, the effectiveness of RB101 can be revealed by preadministration of the CCKB receptor antagonist CI988. Considering the weak **opioid** side effects obtained with RB101 treatment and the strong increase of its effects by the CCKB receptor antagonist, this type of drug combination could have promising therapeutic application in the management of pain in humans.
REFERENCE COUNT: 81 THERE ARE 81 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 90 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1992:441382 CAPLUS
DOCUMENT NUMBER: 117:41382
TITLE: Neuropeptide Y and sigma ligand (JO 1784) suppress stress-induced colonic motor disturbances in rats

through sigma and cholecystokinin receptors
AUTHOR(S): Gue, M.; Junien, J. L.; Del Rio, C.; Bueno, L.
CORPORATE SOURCE: Dep. Pharmacol., Inst. Natl. Rech. Agron., Toulouse, 31931, Fr.
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1992), 261(3), 850-5
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of neuropeptide Y (NPY), sigma ligand (JO 1784) and sulfated cholecystokinin octapeptide (CCK8s) on emotional stress (ES) and ACTH-releasing hormone (CRH)-induced colonic hypermotility were evaluated in rats equipped with chronically implanted electrodes on the colon and a small catheter into the lateral ventricle of the brain. A 139% (97-172%) increase in colonic spike burst frequency was observed in rats placed in a test cage in which they had previously received elec. foot-shocks, an event assimilated to an ES. Intracerebroventricular injection of CRH (0.5 μg/kg) mimicked the effects of ES by increasing colonic spike burst frequency by 89.0%. Given i.c.v., both JO 1784 (0.1 μg/kg) and NPY (0.15 μg/kg) blocked these stimulatory effects. Similarly, i.c.v. administration of CCK8s (0.1 μg/kg) abolished both ES and CRH stimulated colonic motility, an effect reproduced by central injection of JMV 180, a cholecystokinin (CCK) derivative with high affinity for CCKA receptors, (1 μg/kg), but not by JMV 170, a CCK derivative with low affinity for CCKA receptor at similar or higher dose. BMY 14802 (a sigma receptor antagonist) injected s.c. (1 mg/kg) abolished the antagonistic effects of JO 1784 and NPY on the ES-induced colonic hyperkinesia. Injected i.c.v., **devazepide** (L 364, 718), a CCKA receptor antagonist, at 0.1 and 1 μg/kg, abolished the effect of both JO 1784 and NPY; by contrast L365, 260, a CCKB antagonist, required a dose of 10 μg/kg to block the antagonistic effect of NPY and JO 1784. These results suggest that NPY and sigma ligands act through a common receptor at the central nervous system level to block the effects of ES and CRH on colonic motility and that these effects are mediated through the central release of CCK8s and involved more the specific CCKA receptor subtype.

L5 ANSWER 91 OF 166 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 97159181 EMBASE
DOCUMENT NUMBER: 1997159181
TITLE: Cholecystokinin-induced antinociception is not blocked by CCK-A or CCK- B receptor antagonists.
AUTHOR: Williams C.L.; Rosenfeld G.C.; Burks T.F.
CORPORATE SOURCE: Dr. C.L. Williams, Department of Pharmacology, Univ. of Texas Health Science Center, MSB 5.304, P.O. Box 20708, Houston, TX 77225, United States
SOURCE: Peptides, (1997) 18/3 (409-414).
Refs: 28
ISSN: 0196-9781 CODEN: PEPTDO
PUBLISHER IDENT.: S 0196-9781(96)00341-5
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB To determine the relative importance of CCK-A, CCK-B, and **opioid** receptors in mediating the antinociceptive actions of cholecystokinin, we evaluated the actions of selective agonists and antagonists in the mouse hot plate assay. The agonists used were CCK (1-30 nmol ICV), a CCK-A receptor agonist (SNF9019; 0.3-10 nmol ICV), and a CCK-B receptor agonist (SNF9007; 0.3-10 nmol ICV). The antagonists used were the CCK-A receptor antagonist, L364,718 (12.5 nmol ICV), CCK-B receptor antagonist, L365,260 (2.5-25 nmol ICV), and the nonselective **opioid** receptor

antagonist naloxone (1 mg/kg SC). CCK and its receptor-selective analogues, SNF9019 and SNF9007, resulted in antinociception that was blocked by naloxone, but was not antagonized by L364,718 or L365,260. In contrast, in positive control experiments, the inhibitory effects of CCK, SNF9019, and SNF9007 on gastrointestinal propulsion in mice were antagonized by identical ICV does of L364,718 and L365,260. We conclude that centrally administered CCK produces antinociception in the mouse hot plate assay via **opioid** receptors, but independent of CCK-A or CCK-B receptors. It is necessary to speculate that other CCK receptors, not antagonized by currently available selective antagonists, may exist.

L5 ANSWER 92 OF 166 USPATFULL on STN
ACCESSION NUMBER: 2003:85867 USPATFULL
TITLE: Oral delivery formulation
INVENTOR(S): Compton, Bruce Jon, Lexington, MA, UNITED STATES
Solari, Nancy E., West Newton, MA, UNITED STATES
Flangan, Margaret A., Stow, MA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003059471	A1	20030327
APPLICATION INFO.:	US 2001-997277	A1	20011129 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1998-55560, filed on 6 Apr 1998, ABANDONED

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-69501P	19971215 (60)
	US 1998-73867P	19980204 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Stephen J Gaudet, 68H Stiles Road, Salem, NH, 03079
NUMBER OF CLAIMS: 42
EXEMPLARY CLAIM: 1
LINE COUNT: 2950
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Flakes containing drugs and methods for forming and using such flakes are provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 93 OF 166 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2004:375899 BIOSIS
DOCUMENT NUMBER: PREV200400379359
TITLE: **Opioids** as agents of reward-related feeding: a consideration of the evidence.
AUTHOR(S): Levine, Allen S. [Reprint Author]; Billington, Charles J.
CORPORATE SOURCE: Minnesota Obes Ctr, Dept VAMC, 151,1 Vet dr, Minneapolis, MN, 55417, USA
ALLENL@umn.edu
SOURCE: Physiology & Behavior, (August 2004) Vol. 82, No. 1, pp. 57-61. print.
CODEN: PHBHA4. ISSN: 0031-9384.
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 22 Sep 2004
Last Updated on STN: 22 Sep 2004
AB Gerard Smith was one of the pioneers in the field of neuropeptidergic control of food intake. He established methodology and criteria used to determine whether a neuropeptide acts as an endogenous satiety factor. More recently, he theorized that there are direct and indirect controls of meal size. Direct controls include those that depend upon contact of food

with preabsorptive receptors from the tip of the tongue to the end of the small intestine, and indirect controls include those that do not depend upon direct contact of mucosal receptors, such as learning and metabolism. In this review, we consider the evidence that **opioids** are mediators of reward-related feeding. We address these issues adopting Smith's approach to problem solving, including an evaluation of the **opioids** as controllers of the meal. We also present a novel concept of "hedonic restriction," resulting in a change in **opioid** gene expression. Overall, we believe the evidence supporting **opioid** participation in reward-driven and other types of ingestion is very strong, but much work remains before we understand how **opioids** contribute to the widely distributed neural network that controls ingestive behavior. Published by Elsevier Inc.

L5 ANSWER 94 OF 166 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 92104144 EMBASE
DOCUMENT NUMBER: 1992104144
TITLE: Neuropeptides. Function and clinical applications.
AUTHOR: Hughes J.; Woodruff G.N.
CORPORATE SOURCE: Parke-Davis Neuroscience Research Centre, Hills Road, Cambridge, CB2 2QB, United Kingdom
SOURCE: Arzneimittel-Forschung/Drug Research, (1992) 42/2 A (250-255).
ISSN: 0004-4172 CODEN: ARZNAD
COUNTRY: Germany
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 002 Physiology
032 Psychiatry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English; German
AB Neuropeptides are the most abundant chemical messengers in the brain and their major role seems to be the modulation of amine and amino acid neurotransmission. This appears to be achieved at many sites by the co-release of peptide with the primary transmitter. The presynaptic biochemistry and physiology of neuropeptides ensure that neuromodulation is highly plastic with almost infinite adaptive potential. The recent development of novel drugs (termed peptoids) that mimic or block neuropeptide function have opened up new clinical approaches to a number of conditions. Thus high efficacy kappa **opioid**-receptor agonists such as CI-977 (enadoline) have potential for the treatment of pain and stroke whilst the development of highly selective and bioavailable cholecystokinin B (CCK-B) antagonists such as CI-988([R-(R*,R*)]-4-[[2 [[3-(1H-indol- 3-yl)-2-methyl-1-ox6-2-[[tricyclo[3.3.1.1.3.1]dec-2-yloxy)carbonyl]amino]propyl]amino]-1-phenethyl]amino-4-oxobutanoic acid) have offered new insights into the mechanisms underlying and the treatment of anxiety disorders and drug abuse. In general it appears that peptoids may offer a greater selectivity of drug action when compared to amino acid/amine based compounds. Peptoid antagonists appear to be relatively free of side effects possibly because neuropeptide systems are only activated under very selective conditions. Peptoid agonists on the other hand can exert extremely powerful actions on brain function and this may be related to the key position neuropeptide receptors occupy in the hierarchy of chemical communication in the brain.

L5 ANSWER 95 OF 166 MEDLINE on STN
ACCESSION NUMBER: 1999299815 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10372600
TITLE: The evaluation of the role of CCK in the **opioid** modulation of the motility of the gastrointestinal tract in sheep.
AUTHOR: Kania B F; Brikas P; Bueno L; Fioramonti J;

Zaremba-Rutkowska M
CORPORATE SOURCE: Department of Veterinary Pharmacology and Toxicology, Veterinary Faculty, Warsaw Agricultural University SGGW, Poland.. wet_kfit@sggw.waw.pl
SOURCE: Journal of veterinary pharmacology and therapeutics, (1999 Apr) 22 (2) 153-60.
Journal code: 7910920. ISSN: 0140-7783.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 19991101
Last Updated on STN: 20000303
Entered Medline: 19991019

AB The participation of central cholecystokinin-8 (CCK-8) receptors in the modulatory effect of D-Ala2, N-Me-Phe4, Gly5-ol enkephalin (DAGO), a selective mu-**opioid** receptor agonist, on the spike burst activity of the gastrointestinal tract (rumen, reticulum, antrum, duodenum, colon and caecum) in sheep was investigated. DAGO was infused intracerebroventricularly (i.c.v.) at doses of 0.1-1 microg/kg body weight (BW). It was shown that DAGO significantly inhibited myoelectrical activity of the wall of the forestomachs, abomasum and colon but stimulated this activity in the duodenum (rate of myoelectrical migrant complex-MMC). The effects of DAGO were prevented by CCK-8 antagonists (L-364.718 and L-365.260) previously infused at doses of 5-20 microg/kg BW. The results of this present study indicate that central receptors of CCK-8 participated in the modulatory action of an **opioid** on myoelectrical activity of the gastrointestinal tract in sheep. Furthermore, this result suggests that CCK-8 is released in response to mu-receptor stimulation, because CCK-8 antagonists (L-364.718 and L-365.260) prevented the modulatory action of DAGO on the gastrointestinal motility in sheep.

L5 ANSWER 96 OF 166 USPATFULL on STN
ACCESSION NUMBER: 2004:233875 USPATFULL
TITLE: DHA-pharmaceutical agent conjugates of taxanes
INVENTOR(S): Shashoua, Victor E., Brookline, MA, UNITED STATES
Swindell, Charles E., Merion, PA, UNITED STATES
Webb, Nigel L., Bryn Mawr, PA, UNITED STATES
Bradley, Matthews O., Laytonsville, MD, UNITED STATES
PATENT ASSIGNEE(S): Protarga, Inc., King of Prussia, PA (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004180949	A1	20040916
APPLICATION INFO.:	US 2003-618884	A1	20030714 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2001-846838, filed on 1 May 2001, GRANTED, Pat. No. US 6602902 Continuation of Ser. No. US 1998-135291, filed on 17 Aug 1998, ABANDONED Continuation of Ser. No. US 1996-651312, filed on 22 May 1996, GRANTED, Pat. No. US 5795909
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Edward R. Gates, Wolf, Greenfield & Sacks, P.C., 600 Atlantic Avenue, Boston, MA, 02210
NUMBER OF CLAIMS: 19
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 14 Drawing Page(s)
LINE COUNT: 2440
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides conjugates of cis-docosahexaenoic acid and pharmaceutical agents useful in treating noncentral nervous system conditions. Methods for selectively targeting pharmaceutical agents to

desired tissues are provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 97 OF 166 USPATFULL on STN
ACCESSION NUMBER: 2004:139413 USPATFULL
TITLE: Fatty acid-pharmaceutical agent conjugates
INVENTOR(S): Webb, Nigel L., Bryn Mawr, PA, UNITED STATES
Bradley, Matthews O., Laytonsville, MD, UNITED STATES
Swindell, Charles S., Merion, PA, UNITED STATES
Shashoua, Victor E., Brookline, MA, UNITED STATES
PATENT ASSIGNEE(S): Protarga Pharmaceuticals, Inc., King of Prussia, PA (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004106589	A1	20040603
APPLICATION INFO.:	US 2003-455250	A1	20030605 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2000-730450, filed on 5 Dec 2000, GRANTED, Pat. No. US 6576636 Continuation of Ser. No. US 1996-651428, filed on 22 May 1996, ABANDONED
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Edward R. Gates, Wolf, Greenfield & Sacks, P.C., 600 Atlantic Avenue, Boston, MA, 02210
NUMBER OF CLAIMS: 12
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 14 Drawing Page(s)
LINE COUNT: 2524
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention provides conjugates of fatty acids and pharmaceutical agents useful in treating noncentral nervous system conditions. Methods for selectively targeting pharmaceutical agents to desired tissues are provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 98 OF 166 USPATFULL on STN
ACCESSION NUMBER: 2001:90260 USPATFULL
TITLE: Fatty acid-pharmaceutical agent conjugates
INVENTOR(S): Webb, Nigel L., Bryn Mawr, PA, United States
Bradley, Matthews O., Laytonsville, MD, United States
Swindell, Charles S., Merion, PA, United States
Shashoua, Victor E., Brookline, MA, United States

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2001002404	A1	20010531
	US 6576636	B2	20030610
APPLICATION INFO.:	US 2000-730450	A1	20001205 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1996-651428, filed on 22 May 1996, ABANDONED
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Edward R. Gates, Wolf, Greenfield & Sacks, P.C., 600 Atlantic Avenue, Boston, MA, 02210
NUMBER OF CLAIMS: 12
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 14 Drawing Page(s)
LINE COUNT: 2511
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention provides conjugates of fatty acids and pharmaceutical agents useful in treating noncentral nervous system conditions. Methods for selectively targeting pharmaceutical agents to desired tissues are

provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 99 OF 166 USPATFULL on STN

ACCESSION NUMBER:	1998:98932 USPATFULL
TITLE:	DHA-pharmaceutical agent conjugates of taxanes
INVENTOR(S):	Shashoua, Victor E., Brookline, MA, United States Swindell, Charles S., Merion, PA, United States Webb, Nigel L., Bryn Mawr, PA, United States Bradley, Matthews O., Laytonsville, MD, United States
PATENT ASSIGNEE(S):	Neuromedica, Inc., Conshohocken, PA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5795909		19980818	
APPLICATION INFO.:	US 1996-651312		19960522	(8)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Jarvis, William R. A.
LEGAL REPRESENTATIVE:	Wolf, Greenfield & Sacks, P.C.
NUMBER OF CLAIMS:	12
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	27 Drawing Figure(s); 14 Drawing Page(s)
LINE COUNT:	2451

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides conjugates of cis-docosahexaenoic acid and taxanes useful in treating cell proliferative disorders. Conjugates of paclitaxel and docetaxel are preferred.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 100 OF 166 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

ACCESSION NUMBER:	1989:105468 BIOSIS
DOCUMENT NUMBER:	PREV198936050884; BR36:50884
TITLE:	**MORPHINE** ANALGESIA IN THE RAT PAW PRESSURE TEST IS BLOCKED BY CCK BUT POTENTIATED BY THE CCK ANTAGONIST **MK-329**.
AUTHOR(S):	O'NEILL M F [Reprint author]; DOURISH C T; IVERSEN S D
CORPORATE SOURCE:	MERCK SHARP AND DOHME RES LAB, NEUROSCI RES CENT, TERLINGS PARK, EASTWICK ROAD, HARLOW, ESSEX CM20 2QR, UK
SOURCE:	British Journal of Pharmacology, (1988) Vol. 95, No. SUPPL, pp. 505P. Meeting Info.: MEETING OF THE BRITISH PHARMACOLOGICAL SOCIETY, DUBLIN, IRELAND, JULY 6-8, 1988. BR J PHARMACOL. CODEN: BJPCBM. ISSN: 0007-1188.
DOCUMENT TYPE:	Conference; (Meeting)
FILE SEGMENT:	BR
LANGUAGE:	ENGLISH
ENTRY DATE:	Entered STN: 9 Feb 1989 Last Updated on STN: 9 Feb 1989

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